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# Halogenation of Heterocyclic Compounds

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## I. General Considerations

### A. SIGNIFICANCE OF HALOGENATION IN HETEROCYCLIC CHEMISTRY

#### 1. *Synthetic Scope*

The introduction of a halogen atom into the nucleus of an unsaturated heterocycle serves at once as a valuable synthetic route to heterocyclic derivatives and as a revealing probe of substitution processes at unsaturated carbon.<sup>1</sup> From a synthetic standpoint, aromatic and heterocyclic halides have become more attractive starting materials in recent years. Traditionally considered to be rather unreactive, these vinylic halides had been found suitable only in certain reactions

<sup>1</sup> For an excellent treatment of the preparative and mechanistic aspects of aromatic halogenation, cf. P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation." Butterworth, London and Washington, D.C., 1959.

such as: (a) the formation of the Grignard or organolithium reagent; (b) displacement processes at elevated temperatures, usually conducted in the presence of copper salts; or (c) displacements occurring under mild conditions when an electron-withdrawing substituent was situated *ortho* or *para* (alpha or gamma in heterocycles) to the carbon-halogen bond. The introduction of superior reaction solvents for organometallic processes (tetrahydrofuran and the glycol ethers) and displacement reactions (dimethyl sulfoxide and dimethylformamide), as well as an appreciation of the role of benzyne and arylene intermediates in aromatic substitution, promises a far greater importance to these unsaturated halides.

## 2. Mechanistic Importance

A similar situation seems to obtain in our understanding of the mechanisms of heterocyclic halogenation. Although copious research has provided accurate insight into the electrophilic substitution reactions of benzene derivatives, a correspondingly precise knowledge of heterocyclic substitution still is lacking. Admittedly formidable complexities, as the interplay of changing orientation with experimental conditions, the significance of  $n$ - or  $\pi$ -species in the pre-equilibria to reaction, the uncertain role of intermediate covalent addition compounds, and the possibility of rearrangements, remain unresolved. To this already bristling thicket of difficulties may be added the greater number of substitution isomers possible with many heterocyclic systems. It would appear, however, that this latter point may be viewed as an advantage for the researcher hoping to test his grasp of substitution processes at unsaturated carbon. This gradation of electronic environment within the same heterocyclic system permits the distribution of substitution isomers to be viewed as the result of a competition experiment. Hence the many complications mentioned previously can be largely canceled. More recent examination of heterocyclic substitution has demonstrated two valuable points in this connection: first, that the severe conditions of nitration, halogenation, and other substitutions traditionally used with many heterocycles are not necessary for successful reaction; and second, that the orientation displayed by heterocycles is highly dependent upon the polarity of the reagent and the medium.

Counterpoised to these experimental difficulties are certain distinct advantages to studies of heterocyclic halogenation. In the first place, the halogen family comprises a rationally related series of electrophilic

reagents of gradated reactivity and selectivity, running the gamut from the rather inert molecular iodine to the violently reactive fluorine.<sup>2</sup> A second advantage to halogenation as a mechanistic probe is the wide range of solvent polarity and acidity which can be feasibly employed. Pyridinoid heterocycles, for example, can be studied either as the protonated amine (in concentrated sulfuric acid) or as the free base (in carbon tetrachloride) with marked consequences on the rate and orientation of substitution. Third, the resulting orientation and reactivity data obtained from such adaptable halogenation studies can serve as an index of electronic character at different reacting sites in unsaturated heterocycles.

## B. IMPORTANT HALOGENATING AGENTS

### 1. *Neutral Reagents*

Among the customary halogenating agents, the most widely acceptable are molecular chlorine and bromine. Unfortunately, no widely applicable and easily regulated method for limited substitution by elemental fluorine is available.<sup>2</sup> In contrast, the unaided attack of molecular iodine is too slow in many cases. In the latter instance both kinetic and thermodynamic factors (reversal by the hydrogen iodide by-product) conspire against a fruitful iodination. Table 1 lists certain properties of particular interest for some halogen and interhalogen molecules. The relatively weak bonds in molecular fluorine and iodine predispose these halogens to homolytic processes. In addition, the oxidizing action of the elemental halogen also comes to the fore with these same members: with fluorine, because of its high oxidizing power; with iodine, because its lower halogenating action permits the competing oxidation to become prominent. Finally, the relative acidities of the halogens, as exhibited toward the chloride ion, give some indication of their tendency to form  $n$ - or  $\pi$ -adducts with heterocyclic bases.

Although nonsolvating media of low polarity are sometimes suitable for reactive heterocycles, more often polar or basic solvents such as

<sup>2</sup> Although controlled substitution with molecular fluorine is difficult to attain, noteworthy is the recent success in perfluorinating both saturated and unsaturated heterocycles by electrolysis in anhydrous hydrogen fluoride. Cf. T. C. Simmons and F. W. Hoffmann, *J. Am. Chem. Soc.* **79**, 3429 (1957), for the preparation of undecafluoropiperidine (from piperidine). The latter compound can be converted into pentafluoropyridine by passing it over an iron contact at 600° [R. E. Banks, A. E. Ginsberg, and R. N. Haszeldine, *J. Chem. Soc.* p. 1740 (1961)].

TABLE I  
PROPERTIES OF CERTAIN HALOGEN MOLECULES

Property	F <sub>2</sub>	Cl <sub>2</sub>	Br <sub>2</sub>	I <sub>2</sub>	ICl
Molecular weight	38.0	70.9	160	254	162
Boiling point (°C)	-187	-35	59	184	97
Bond energy (kcal/mole)	38	58	46	36	50
Bond length (Å)	1.44	1.98	2.28	2.66	—
Electronegativity of X	3.90	3.15	2.95	2.65	—
Electron affinity of X (kcal/gm-atom)	83.5	87	82	75	—
Acid strength toward aqueous Cl <sup>-</sup> ( $-\Delta F^\circ$ ) <sup>a</sup>	—	4.4	0.04	-1.14	-5.7
Oxidation potential of X <sup>0</sup> (H <sub>2</sub> O)	-2.85	1.36	1.09	0.54	—

<sup>a</sup> R. L. Scott, *J. Am. Chem. Soc.* **75**, 1550 (1953).

ethyl ether, 1,4-dioxane, ethanol, acetic anhydride, glacial acetic acid, chloroform, and water are desirable. For media of low polarity small added amounts of ethers and amines appear to catalyze the halogenation process.<sup>3</sup> That 1:1 halogen adducts of ethers (dioxane·Br<sub>2</sub>) and of amines (pyridine·I<sub>2</sub>) have been characterized tends to implicate halogen complexes as the catalytically significant species in these cases.<sup>4</sup>

## 2. Sources of Positive Halogen

To catalyze the attack on certain heterocycles, the halogen may be supplemented by a Lewis acid. Granted that the mechanistic details of these so-called "positive" halogenations are supported only by circumstantial evidence, the generation of a complexed X<sup>+</sup> or the radical X· seems to be involved. Aluminum and ferric halides, silver salts, and possibly solutions of halogen in concentrated or fuming sulfuric acid appear to be cases in point. Other potential sources of "positive" halogen are the interhalogen compounds (BrCl, BrI, ICl) and CF<sub>3</sub>CO<sub>2</sub>X, *tert*-C<sub>4</sub>H<sub>9</sub>OCl, SOCl<sub>2</sub>, and SO<sub>2</sub>Cl<sub>2</sub>, but little is known about their detailed behavior. Recent studies on the halogenation of

<sup>3</sup> R. Pajeau, *Bull. Soc. Chim. France* p. 621 (1961); cf. A. P. Terent'ev, L. I. Belen'kii, and L. A. Yanovskaya, *Zh. Obshch. Khim.* **24**, 1265 (1954); see *Chem. Abstr.* **49**, 12327 (1955) for brominations effected by dioxane dibromide.

<sup>4</sup> O. Hassel, *Dansk Tidsskr. Farm.* **36**, 41 (1962); see *Chem. Abstr.* **57**, 9228 (1963).

methyl pyrrole-2-carboxylate suggest that the selective chlorination at C-5 with *tert*-butyl hypochlorite is due to a radical process. The indiscriminate attack at C-4 and C-5 by molecular chlorine and by sulfonyl chloride in the presence of peroxides indicates the importance of both polar and radical processes.<sup>4a</sup> On the other hand, halogenations

TABLE II  
HETEROCYCLIC HALOGENATION PROCEDURES

Neutral
$X_2$ ( $Cl_2$ , $Br_2$ , $I_2$ , $ICl$ ) in $CHCl_3$ , $CCl_4$ , $CS_2$ , $C_6H_6$ , $ROR$ , or $ROH$ with $HX$ scavenger: $MCO_3$ , $HgO$ , $R_2SO$ , $MOAc$ $\begin{array}{c} O \\    \\ X-N(C-R)_nH_{2-n} \end{array}$ in $CCl_4$ $SOX_2$ , $SO_2X_2$ , $PCl_5$ , <i>tert</i> - $C_4H_9OCl$
Acidic
$X_2$ ( $Cl_2$ , $Br_2$ , $I_2$ ) in $HOH$ , $ROH$ , $RCOOH$ , $(RCO)_2O$ $X_2$ in conc. $H_2SO_4$ or $H_2S_2O_7$ with or without $Ag_2SO_4$ $X_2$ with $Al_2X_6$ , $AgOAc$ $X_2$ with acidic oxidant: $HXO_3$ , $HNO_3$ $\begin{array}{c} O \\    \\ X-N(C-R)_nH_{2-n} \end{array}$ with $Al_2X_6$ , $Fe_2X_6$ $HX$ with oxidizing conditions: $H_2O_2$ , $R_2SO$ , anodic electrolysis $HOX$ or $PCl_5$
Basic
$X_2$ ( $Cl_2$ , $Br_2$ , $I_2$ ) in aqueous solution with $R_3N$ , $NaOH$ , $NaOAc$ , $Na_2CO_3$ $X_2$ added to preformed metallic salt, $M-R$ , prepared from $R-H + MR'$ , $MH$ , $MOH$ , or $MOR$

by solutions of hypohalous acids have been shown by kinetic studies to involve "positive" halogen species ( $X^+$  in its solvated forms,  $X-OH_2^+$ ,  $X-OHR^+$ , or  $X-NR_3^+$ ). By and large, then, similar

<sup>4a</sup> P. Hodge and R. W. Rickards, *J. Chem. Soc.* p. 459 (1965).

moieties seem important in the halogenating action of *N*-haloamides (*N*-bromosuccinimide) and acyl hypohalites ( $\text{CH}_3\text{CO}_2\text{X}$ ) in aqueous solution.

Less explored halogenation methods of promise involve the use of *N*-haloamides in nonaqueous media and the combination of an alkyl or hydrogen halide with an oxidizing agent. Despite their wide acceptance as reagents for allylic bromination, the *N*-haloamides (*N*-bromosuccinimide, *N*-haloacetamides, and *N*-halohydantoins) have not been utilized to their full in aromatic nuclear substitution.<sup>5</sup> The controlled halogenation by the use of sulfoxides or peroxides with hydrogen halides<sup>6</sup> or alkyl halides<sup>7</sup> generates the actual halogenating agent *in situ* (solvated  $\text{X}^+$  or  $\text{X}_2$ ). This permits the substitution of sensitive, reactive nuclei under mild conditions without a large excess of reagent. In Table II are compiled some of the most important halogenating agents for heterocyclic systems and their appropriate experimental conditions.

### 3. Individuating Character of the Heterocycle

In closing this brief survey of halogenating agents, comment is in place on the role which the specific heterocycle plays in the choice of halogenating agent. The hydrogen halide liberated in the halogenation may interfere in two ways. Either it may protonate some of the unreacted heterocycle, thereby depressing or changing the nuclear reactivity, or it may cause reversal of the halogenation process. Consequently, the inclusion of hydrogen halide scavengers is desirable; these may be bases ( $\text{NaHCO}_3$ ,  $\text{NaC}_2\text{H}_3\text{O}_2$ ,  $\text{CaCO}_3$ , or  $\text{R}_3\text{N}$ ) or oxidizing agents ( $\text{HNO}_3$ ,  $\text{HXO}_3$ , or  $\text{SO}_3$ ). Occasionally, the change in the heterocycle's orientation upon protonation may be turned to preparative advantage. Witness the following reactions in which substitution occurs exclusively in the pyridinoid<sup>8</sup> or benzenoid<sup>9</sup> ring, depending upon the acidity of the medium [Eqs. (1) and (2)]:

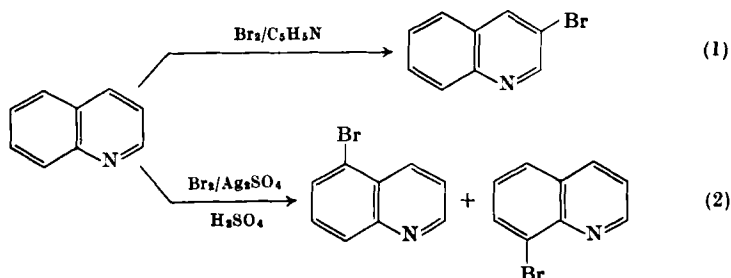
<sup>5</sup> See, e.g., Ng. Ph. Buu-Hoi and J. Lecocq, *Compt. Rend.* **222**, 1441 (1946); **226**, 87 (1948); H. Schmid, *Helv. Chim. Acta* **29**, 573 (1946).

<sup>6</sup> H. Gilman and J. Eisch, *J. Am. Chem. Soc.* **77**, 3862 (1955).

<sup>7</sup> B. C. Saunders and B. P. Stark, *Tetrahedron* **4**, 169 (1958); T. L. Patterson and H. L. Pan, *J. Am. Chem. Soc.* **78**, 4812 (1956); *Chem. Ind. (London)* p. 660 (1957).

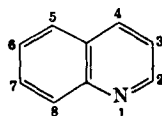
<sup>8</sup> J. J. Eisch, *Chem. Ind. (London)* p. 1449 (1959); *J. Org. Chem.* **27**, 1318 (1962).

<sup>9</sup> P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *Chem. Ind. (London)* p. 361 (1958); *J. Chem. Soc.* p. 561 (1960).



With heterocycles possessing fairly acidic hydrogens (e.g., pyrroles, indoles, and imidazoles), highly basic conditions may lead to halogenation via the conjugate base of the heterocycle. An appealing modification for preparative halogenation then would seem to be the

TABLE III  
THE VARIEGATED BROMINATION OF QUINOLINE



Product (yield, %)	Conditions
1-Dibromide (ca 100)	Br <sub>2</sub> in cold CCl <sub>4</sub> <sup>a</sup>
2-Bromo (50-60)	Br <sub>2</sub> in vapor phase at 500° <sup>b</sup>
3-Bromo (91)	Br <sub>2</sub> in hot CCl <sub>4</sub> with C <sub>5</sub> H <sub>5</sub> N <sup>c</sup>
4-Bromo <sup>d</sup>	3-Bromoquinoline · HBr at 300° <sup>e</sup>
5-Bromo (28)	Br <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>
6-Bromo (ca 2) <sup>g</sup>	Br <sub>2</sub> in hot CCl <sub>4</sub> with C <sub>5</sub> H <sub>5</sub> N <sup>c</sup>
8-Bromo (29)	Br <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>
3,6-Dibromo (35)	Br <sub>2</sub> in glacial HOAc <sup>c</sup>
5,8-Dibromo (43)	2Br <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>
3,6,8-Tribromo	Br <sub>2</sub> in glacial HOAc <sup>c</sup>
5,6,8-Tribromo	3Br <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>

<sup>a</sup> J. J. Eisch, *Chem. Ind. (London)* p. 1449 (1959).

<sup>b</sup> H. E. Jansen and J. P. Wibaut, *Rec. Trav. Chim.* **56**, 699 (1937).

<sup>c</sup> J. J. Eisch, *J. Org. Chem.* **27**, 1318 (1962).

<sup>d</sup> A 38% yield of quinoline was realized.

<sup>e</sup> J. J. Eisch, *J. Org. Chem.* **27**, 4682 (1962).

<sup>f</sup> P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.* p. 561 (1960).

<sup>g</sup> Presumed precursor of 3,6-dibromoquinoline.

irreversible generation of the conjugate base and the addition of a halogen source<sup>10</sup> [Eq. (3), cf. Section II, C, 1]:



To stress the variation in site of substitution possible with a given heterocycle consider the response of quinoline under the different conditions shown in Table III. The results also exemplify other intriguing aspects of halogenation, such as reversibility, temperature coefficient, and metal salt catalysis. These will be discussed in Sections II, C, 3 and III, C.

### C. CURRENT RESEARCH EMPHASIS AND THE SCOPE OF THIS REVIEW

Appreciable recent effort has been devoted to developing highly selective methods for halogenating heterocycles. The method of Derbyshire and Waters (halogen, silver sulfate, and concentrated sulfuric acid)<sup>11</sup> has been applied to quinoline<sup>9</sup> giving results in agreement with nitration. Quite similar orientation patterns in halogenation have been obtained with quinoline and isoquinoline by use of stoichiometric amounts of aluminum chloride.<sup>12</sup> The reductive halogenation of sulfoxides with hydrohalic acids has special appeal for the substitution of cyclic sulfides.<sup>6</sup> The vapor phase halogenation of heterocycles under improved contact catalysis appears to be an attractive approach to desired isomers, if decomposition and rearrangements are minimized.

The complexity of individual halogenation mechanisms has become clear in more recent years from the diverse isomer distributions observed under different reaction conditions. Quantitative product studies are beginning to make a welcome appearance, but kinetic studies are almost wholly lacking. The recent kinetic work on the iodination of imidazole may signal the onset of improvement in this aspect. On the theoretical side, much attention has been given to the several possible quantum mechanical approximations applicable to heterocyclic substitution. Here again the lack of ample quantitative

<sup>10</sup> V. Franzen, *Ber.* **87**, 1148 (1954).

<sup>11</sup> D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* pp. 564 and 574 (1950).

<sup>12</sup> M. Gordon and D. E. Pearson, *J. Org. Chem.* **29**, 329 (1964).



data seems not to give these theoretical views enough rope with which to hang or to save themselves.

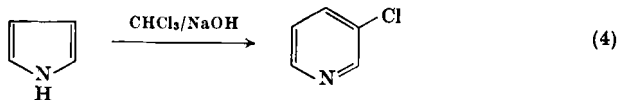
In this survey the emphasis will be placed upon the newer findings in the synthetic and mechanistic aspects of heterocyclic halogenation. As to mechanisms, it appears both necessary and desirable to outline possible views among which present knowledge cannot decide. Hopefully the enthusiasm and curiosity of chemists will be awakened when they appreciate the many unresolved problems in heterocyclic halogenation.

## II. Preparation of Halogen Derivatives

### A. GROSS TRANSFORMATIONS

The classical ambiguity between direct substitution on an aromatic system and substitution via an addition-elimination pathway [Eq. (16), Section III, A] persists for the halogenation of heterocycles under conditions of low polarity. Indeed, with suitable heterocyclic nuclei the three possibilities of substitution, addition, and addition-elimination have all been observed. From existing evidence one cannot assign as yet relative importance to these limiting cases in halogenation mechanisms. However, experimental conditions often can be regulated to favor one or other process for preparative success. These three processes will receive our attention in this review.

Of lesser relevance to this discussion are halogenation methods involving the modification of the carbon skeleton (synthesis and degradation). The Hunsdiecker reaction, as applied to certain heterocyclic acids, has had limited application for the synthesis of halogen derivatives. The preparation of 3-bromo-4,6-dimethyl-2-pyridone from the silver salt of the respective 3-carboxylic acid by treatment with bromine in carbon tetrachloride is a rare example of success.<sup>13</sup> The interaction of carbenes with heterocycles also has been employed infrequently, but recent advances in carbene generation may reactivate this approach.<sup>14</sup> The Ciamician-Dennstedt ring expansion of pyrrole to  $\beta$ -halopyridines is a case in point<sup>15</sup> [Eq. (4)]:



<sup>13</sup> R. G. Johnson and R. K. Ingham, *Chem. Rev.* **56**, 247 (1956).

<sup>14</sup> J. Hine, "Divalent Carbon." Ronald Press, New York, 1964.

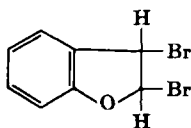
<sup>15</sup> Cf. G. L. Closs and G. M. Schwartz, *J. Org. Chem.* **26**, 2609 (1961).

These and other methods of introducing halogen into heterocycles, such as the transformation of  $\alpha$ - and  $\gamma$ -hydroxypyridinoid bases with inorganic acid halides, the treatment of pyridinoid *N*-oxides with sulfur or phosphorus halides, and the decomposition of diazonium compounds, are treated adequately in existing references.

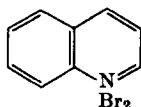
## B. ADDITION PROCESSES

### 1. Types of Adduction

A posteriori, the addition of halogen to heterocycles can ensue in at least three distinct fashions, exemplified by the following adduct types: (a) covalent bonding of halogen to carbon with the partial or complete saturation of the ring<sup>16</sup> (1); (b) *n*-complexation of the halogen at the hetero atom<sup>4, 17</sup> (2); and (c)  $\pi$ -complexation of the molecular halogen<sup>18</sup> (3). Whereas *n* and  $\pi$  types of adduction occur



(1)



(2)



(3)

with extreme ease, the covalent fixation of halogen may require photochemical or radical source promotion. Molecular chlorine dissolved in carbon tetrachloride, in conjunction with illumination and iodine promoter, constitutes a successful set of conditions for many cases,<sup>19, 19a, b</sup> More polar solvents and elevated temperatures often cause the decomposition of intermediate adducts, either by hydrogen halide elimination<sup>20</sup> [Eq. (5)] or by solvolytic substitution<sup>21</sup> [Eq. (6)]:

<sup>16</sup> R. Stoermer and B. Kahlert, *Ber.* **35**, 1633 (1902).

<sup>17</sup> J. J. Eisch and B. Jaselskis, *J. Org. Chem.* **28**, 2865 (1963).

<sup>18</sup> R. P. Lang, *J. Am. Chem. Soc.* **84**, 4439 (1962).

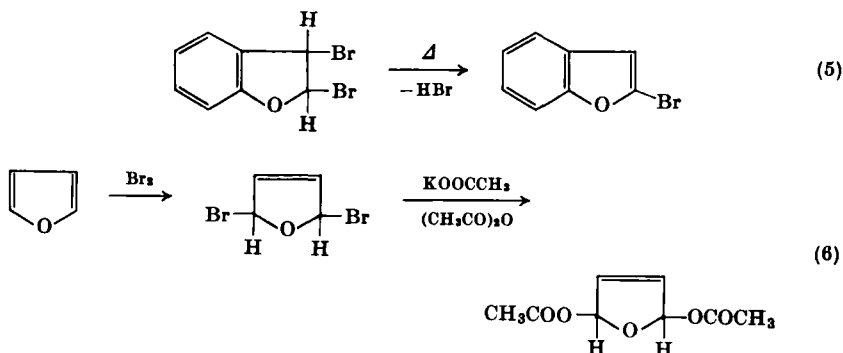
<sup>19</sup> See, e.g., S. Maffei, S. Pietra, and A. Cattaneo, *Gazz. Chim. Ital.* **83**, 812 (1953).

<sup>19a</sup> A. Cattaneo, *Farmaco (Pavia), Ed. Sci.* **12**, 930 (1957); see *Chem. Abstr.* **52**, 11850 (1958).

<sup>19b</sup> C. Bodea and M. Raileanu, *Ann.* **631**, 194 (1960).

<sup>20</sup> H. L. Coonradt and H. D. Hartough, *J. Am. Chem. Soc.* **70**, 1158 (1948); R. Pieck and J. C. Jungers, *Bull. Soc. Chim. Belges* **60**, 357 (1951).

<sup>21</sup> N. Clauson-Kaas, S.-O. Li, and N. Elming, *Acta Chem. Scand.* **4**, 1233 (1950).



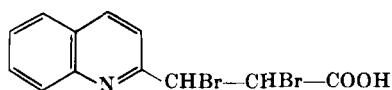
The kinetic significance of these adducts in the ultimate substitution is at present uncertain. Indeed, the isolation of covalent halogen adducts and substitution products from the same system is no compelling proof for a sequential connection. Price's investigation of the bromination of phenanthrene has revealed the importance of this distinction in kinetic studies.<sup>22</sup> The same caveat applies with even greater force to the detectable  $n$ - and  $\pi$ -halogen adducts of heterocycles. Since such adducts are readily dissociable into their components, the establishment of their role in halogenation substitution processes requires far more convincing evidence than a mere proof of their existence in the reacting medium.

## 2. Covalent Adducts

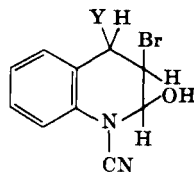
With the foregoing reservations in mind about the relation of such adducts to heterocyclic substitution, it is of interest to inquire about the structure and behavior of these halogen adducts. As to the covalent halogen adducts of heterocycles, the site of attachment, but not the stereochemistry of addition, is known for a number of ring systems (e.g., the dibromide of benzofuran<sup>16</sup> and the tetradecachloride of acridine<sup>19b</sup>). The *cis* or *trans* location of vicinal halogens would be of importance in any future studies of substitution via addition-elimination pathways. Two instances of adduction of possible relevance to heterocyclic halogenation might have stereochemical implications. First, the dibromide of quinaldinic acid (4) undergoes principally dehalogenation rather than dehydrobromination or decarboxylative debromination when treated with base.<sup>23</sup> Possibly

<sup>22</sup> C. C. Price, *Chem. Rev.* **29**, 37 (1941).

<sup>23</sup> A. A. Alberts and G. B. Bachman, *J. Am. Chem. Soc.* **57**, 1284 (1935).

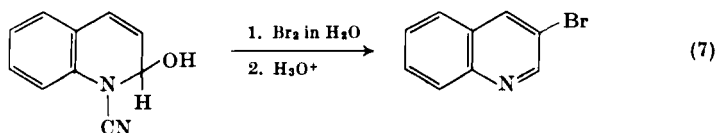


(4)



(5)

the *trans* adduct has little tendency to form the rotamer necessary for dehydrobromination. In any event, bromine addition  $\alpha,\beta$ - to  $C=N$  does not lend itself to bromination by substitution, and this tends to weaken the necessity of bromine addition to C-3, C-4 (also  $\alpha,\beta$ - to  $C=N$ ) to permit the observed C-3 bromination of quinoline itself. In the second case, intermediate adducts (5) have been detected when 2-hydroxy-1-cyano-1,2-dihydroquinoline is treated with bromine in buffered, aqueous methanol.<sup>24</sup> Since the isomeric adducts (5) yield



(7)

3-bromoquinoline upon treatment with acid [Eq. (7)], this has been adduced as evidence in favor of 1,2-adduction for the bromination of quinoline itself. However, the failure to detect corresponding covalent adducts in the bromination of quinoline under varying conditions of polarity makes such a viewpoint of doubtful generality.

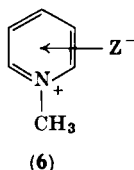
### 3. Relation of *n*- and $\pi$ -Adducts

Considerable attention has been devoted to ascertaining the nature of heterocyclic *n*- and  $\pi$ -complexes with the halogens, especially iodine.<sup>25</sup> Generally the halogen molecule ( $I_2$ ,  $Br_2$ ,  $IX_n$ ) is thought to be the Lewis acid or electron acceptor. The basic character of the heterocycle may stem from any unshared electron pairs on the heteroatom (*n*-complex) or from the unsaturation of the ring ( $\pi$ -complex). Although the halogen appears to function as electron pair acceptors in many such 1:1 complexes, there are indications that

<sup>24</sup> P. B. D. de la Mare, M. D. Johnson, and J. H. Ridd, *Chem. Ind. (London)* p. 1505 (1960); M. D. Johnson and J. H. Ridd, *J. Chem. Soc.* p. 291 (1962).

<sup>25</sup> L. J. Andrews and R. M. Keefer, *Advan. Inorg. Chem. Radiochem.* **3**, 91 (1961).

halogen molecules and polyhalide ions may serve as  $\pi$ -donors, especially toward positively polarized heterocycles. Spectral evidence for this type of interaction in pyridine methiodide has been reported recently<sup>26</sup> and it is appealing to suggest that similar interactions may occur in heterocycle complexes with several halogen molecules<sup>27</sup> (e.g., acridine  $\cdot 5\text{Br}_2$ ) or in quaternary polyhalide salts (e.g., quino-line  $\cdot \text{HBr} \cdot 2\text{Br}_2$ ).<sup>17, 28</sup> Since the charge-transfer structures of type 6 have been implicated in nucleophilic attack on pyridinoid rings, they may prove to have a significant role in halogenations of the pyridinoid



nucleus at high temperatures (e.g., the bromination of quinoline at C-3 by the heating of *n*-propylquinoline tribromide).

#### 4. Nature of *n*-Adducts

The structure of *n*-complexes has been examined by the X-ray crystallographic studies of solid samples and by the spectral measurement of heterocycle-halogen equilibria in solution. By the former approach the structure of the solid 1:2 pyridine-molecular iodine complex has been shown to consist principally of two pyridine molecules collinearly bonded to an iodine atom and of linear triiodide units. Moreover, in the 1:1 complex of dioxane and bromine, the heterocyclic oxygen-bromine-bromine linkages are also collinear.<sup>4</sup> In the latter type of study, interest in the well-known phenomenon of "brown" iodine solutions has occasioned the measurement of the stability constants for many complexes of halogen and heterocycles.<sup>25, 29</sup> Information concerning their structure in solution comes from a consideration of the relative size of such constants as a function of heterocycle structure. Thus, the fact that bromine complexes of both 8-bromo- and 8-methylquinolines possess stability constants ( $K = 1.1$  and  $4.8$  liters/mole) much smaller than that of quinoline itself

<sup>26</sup> E. M. Kosower and P. E. Klinedinst, Jr., *J. Am. Chem. Soc.* **78**, 3493 (1956).

<sup>27</sup> W. Slough and A. R. Ubbelohde, *J. Chem. Soc.* pp. 911 and 982 (1957).

<sup>28</sup> P. F. Trowbridge, *J. Am. Chem. Soc.* **21**, 66 (1899).

<sup>29</sup> A. I. Popov and R. H. Rygg, *J. Am. Chem. Soc.* **79**, 570, 4622 (1957).

( $K = 116$  liters/mole) argues very strongly for an  $n$  type of complex where the bromine molecule lies in the plane of the heterocyclic ring. This variation cannot be ascribed principally to inductive influences of the C-8 substituent, where a methyl group enhances the  $\pi$ -basicity and  $n$ -basicity of aromatic systems in the absence of steric effects.<sup>17</sup> The results of similar studies with iodine complexes of various heterocyclic bases are presented in Table IV. The smaller  $K$  for 2,6-dimethylpyridine (26.23) compared with that of pyridine (43.74), and indeed

TABLE IV  
STABILITY CONSTANTS OF IODINE COMPLEXES WITH  
HETEROCYCLES<sup>a</sup>

Heterocycle	Stability constant <sup>b</sup>	p <i>K</i> <sub>a</sub>
Pyridine · I <sub>2</sub>	43.7 <sup>c</sup>	5.17
2-Picoline · I <sub>2</sub>	50.0	5.97
2,6-Lutidine · I <sub>2</sub>	26.3	6.75
2,4,6-Collidine · I <sub>2</sub>	52.0	7.59
Quinoline · I <sub>2</sub>	69.0	4.85
Isoquinoline · I <sub>2</sub>	39.4	5.14
Phenanthridine · I <sub>2</sub>	36.4	4.42
7,8-Benzoquinoline	—	4.25

<sup>a</sup> J. N. Chaudhuri and S. Basu, *Trans. Faraday Soc.* **55**, 898 (1959).

<sup>b</sup> Measurements performed in pure CHCl<sub>3</sub> at 28°.

<sup>c</sup> A. G. Maki and E. K. Plyler, *J. Phys. Chem.* **66**, 766 (1962), report a value of 107 in cyclohexane; A. I. Popov and R. H. Rygg, *J. Am. Chem. Soc.* **79**, 4622 (1957), found a value of 101 in CCl<sub>4</sub>.

the failure of 7,8-benzoquinoline to form any detectable complex, are in compelling accord with the  $n$ -type model.<sup>30</sup> This view contrasts with the interpretation given to recent conductimetric and spectral data on benzoquinoline-bromine adducts. From bromine adducts of the type, R<sub>3</sub>N · (Br<sub>2</sub>)<sub>x</sub>, where  $x = 1-5$ , it was argued that some, and probably all, halogen must be held in a  $\pi$  manner.<sup>27</sup> However, it seems more plausible that the first molecule would be bonded in an  $n$  fashion.<sup>17, 31</sup>

<sup>30</sup> J. N. Chaudhuri and S. Basu, *Trans. Faraday Soc.* **55**, 898 (1959).

<sup>31</sup> Cf. R. M. Acheson, T. G. Hoult, and K. A. Barnard, *J. Chem. Soc.* p. 4142 (1954), for a qualitative spectral study of the acridine-bromine system in CHCl<sub>3</sub>.

Spectrophotometric investigations of halogen complexes are prone to interference by substitution reactions occurring with the heterocycle or the solvent. Since this light-catalyzed side reaction produces polyhalide anions, inert solvents of the perhaloalkane type are preferable. For example, solutions of bromine in chloroform give rise to hydrogen bromide rather easily. Likewise, iodine dissolved in pyridine or in quinoline for some time displays a prominent band at 375  $m\mu$  ascribable to the triiodide ion. Freshly prepared iodine solutions in pyridine exhibit strong bands at 320 and 390  $m\mu$ .<sup>32</sup> The former absorption suggests the presence of  $C_5H_5N \cdots I^+ \cdots I^-$  ion pairs, since pyridine salts of unipositive iodine,  $C_5H_5-I^+ \cdots Z^-$  ( $Z$  = nitrate, toluate, *p*-chlorobenzoate), all absorb near 320  $m\mu$ . The band at 390  $m\mu$  may be a charge-transfer band for the pyridine-iodine system



(others report 406  $m\mu$ <sup>29</sup>). Whether the spectra of the aged solutions are also due to the equilibrium [Eq. (8)] or whether the marked changes in absorption and conductivity betoken an unknown reaction<sup>33</sup> cannot now be decided. Nevertheless, the characterization of isolated complexes both of unipositive iodine [(pyridine)<sub>2</sub>INO<sub>3</sub>, (pyridine)<sub>2</sub>IClO<sub>4</sub>, and (pyridine)IOCOCC<sub>6</sub>H<sub>5</sub><sup>32</sup>] and of bromine [(pyridine)<sub>2</sub>BrClO<sub>4</sub>, (quinoline)<sub>2</sub>BrClO<sub>4</sub>, and (isoquinoline)<sub>2</sub>BrClO<sub>4</sub><sup>34</sup>] supports their occurrence as solution species. Taking account of the structure of the solid pyridine · 2I<sub>2</sub> complex,<sup>4</sup> one might entertain the ion pair (pyridine)<sub>2</sub>X<sup>+</sup>X<sub>3</sub><sup>-</sup> as a reasonable solution model for 1:1 complexes. The aforementioned study of iodine in pyridine<sup>32</sup> might involve initially an intimate ion pair, (pyridine)I<sup>+</sup>...I<sup>-</sup> (A), which slowly solvolyzes to yield (pyridine)<sub>2</sub>I<sup>+</sup>...I<sub>3</sub><sup>-</sup> (B). Dilute solutions of the components in solvents of low polarity (hexane, carbon tetrachloride) presumably form only *n*-complexes of type A.<sup>29</sup> A recent investigation of bromine-quinoline complexation in carbon tetrachloride revealed the sole formation of 1:1 complexes, even when a twentyfold excess of quinoline was employed.<sup>17</sup> Choice between the stoichiometrically equivalent

<sup>32</sup> R. A. Zingaro, C. A. Vander Werf, and J. Kleinberg, *J. Am. Chem. Soc.* **73**, 88 (1951).

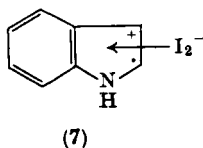
<sup>33</sup> C. H. Park, *J. Korean Chem. Soc.* **6**, 69 (1962); see *Chem. Abstr.* **58**, 6247 (1963).

<sup>34</sup> P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *Chem. Ind. (London)* p. 727 (1959).

alternatives,  $(\text{quinoline})_2\text{Br}^+\dots\text{Br}_3^-$  and  $(\text{quinoline})\text{Br}^+\dots\text{Br}^-$ , could be made by the absence of the typical tribromide absorption in the spectrum of the complex.

### 5. Evidence for $\pi$ -Adducts

Whereas relatively basic aza-aromatic heterocycles and saturated cyclic ethers and sulfides tend to form chiefly  $n$ -halogen complexes, unsaturated heterocycles of low basicity may favor  $\pi$ -complexation. Even with aza-aromatic rings the steric inhibition of  $n$ -complexation at the nitrogen,<sup>17, 30</sup> coupled with increased  $\pi$ -conjugation in higher members, should promote  $\pi$ -donation.<sup>27</sup> The iodine complexes of pyrroles, furans, and thiophenes, which show two prominent charge-transfer ultraviolet bands, are considerably weaker than those of the corresponding saturated heterocycles.<sup>18</sup> Although the structures are not known with certainty,  $\pi$ -complexation may be involved. In a more informative study, indoles have been observed to form solid iodine complexes which display an electron spin resonance signal implicating C-2 and C-3 in the distribution of the unpaired electron spin.<sup>35</sup> With the assumption of the electron donation by indole this may signify the generation of a radical cation (7):



## C. SUBSTITUTION PROCESSES

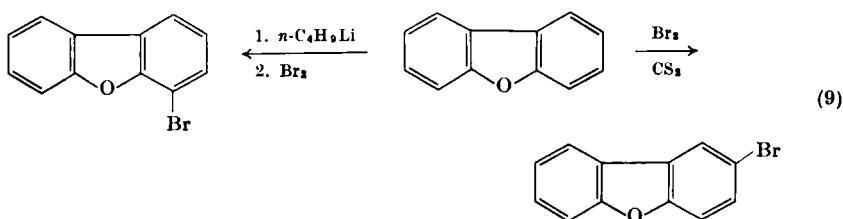
### 1. Direct vs Indirect Halogenation

In the widest sense, heterocyclic halogenation by substitution embraces the introduction of halogen in place of such groups as hydrogen, metal, carboxylate, amino, and hydroxyl (cf. Section II, A). Because of their preparative generality and mechanistic similarity, the cleavage of carbon-hydrogen and carbon-metal bonds by halogenating agents will receive our chief attention in this section. For synthetic purposes, direct halogenation of the heterocycle is complemented nicely by the metalation approach to halogen

<sup>35</sup> A. E. Szent-Györgyi and I. Isenberg, *Proc. Natl. Acad. Sci. U.S.* **46**, 1334 (1960); see *Chem. Abstr.* **55**, 5133 (1961).



derivatives. The different orientations in the two processes permit isomeric halogen derivatives to be synthesized from the same heterocycle. The syntheses of the 2- and 4-bromodibenzofurans illustrate



the synthetic advantages of the two methods. A detailed discussion of the metalation of heterocycles by organolithium reagents is available for interested researchers<sup>36</sup>; hence the metalation reaction will not be elaborated upon here.

## 2. Orientation Patterns

The replacement of hydrogen in heterocycles by halogen has been effected under rather diverse experimental conditions. As a supplement to the previous discussion of halogenating agents (Section I, B), Table V presents the halogenating conditions commonly employed for preparing halogen derivatives of the most important heterocyclic nuclei. Since these data often were gathered in the course of routine synthetic work, few results are as quantitative in accounting for major and minor products as modern analytical techniques would permit. Also, recent findings have demonstrated that older procedures for heterocyclic halogenation were unnecessarily severe. The sensitivity of the site of halogenation to experimental conditions, as is obvious from Table V, introduces the uncertainty as to whether kinetic or thermodynamic factors are operative in high-temperature reactions (cf. Section III, C, 3).

At least semiquantitative data on the isomer distribution for the halogenation of a given unsaturated heterocycle have been reported, although no quantitative comparisons of the relative reactivities of different heterocycles are available. As a prelude to examining possible theoretical correlations between the observed site of halogenation and a heterocycle's electronic structure, it is useful to discern

<sup>36</sup> H. Gilman and J. W. Morton, Jr., *Org. Reactions* 8, 258 (1954).

TABLE V  
THE HALOGENATION OF HETEROCYCLIC NUCLEI

Heterocycle	Halogenating agent	Position of attack <sup>a</sup>	Reference
1. Parent Nuclei			
Furan	Br <sub>2</sub> in CCl <sub>4</sub>	2-Bromo 2,5-Dibromo	37
Thiophen	Cl <sub>2</sub> , Br <sub>2</sub> , or I <sub>2</sub> (HgO)	2-Halo 2,5-Dihalo	38
Pyrrole	Br <sub>2</sub> (750°)	3-Bromo	39
Thiazole	KI <sub>3</sub> in C <sub>2</sub> H <sub>5</sub> OH	Tetraiodo	7, 40
Imidazole	NBS <sup>b</sup>	2-Bromo	41
	KI <sub>3</sub>	2-Iodo	42-44
	Br <sub>2</sub>	4(5)-Bromo	45
Pyrazole	Br <sub>2</sub> , Cl <sub>2</sub> , I <sub>2</sub>	4-Halo	46
Triazole (1,2,3)	Br <sub>2</sub>	4-Bromo	47
Pyridine	Cl <sub>2</sub> (200°) or Br <sub>2</sub> (300°)	3-Halo	48
	Cl <sub>2</sub> (Al <sub>2</sub> Cl <sub>6</sub> )	3,5-Dihalo	49
	Cl <sub>2</sub> (270°) or Br <sub>2</sub> (500°)	2-Halo 2,6-Dihalo	48
	Br <sub>2</sub> (130°) in fuming sulfuric acid	3-Bromo	49a

<sup>37</sup> Cf. H. Gilman and G. F. Wright, *Chem. Rev.* **11**, 323 (1932).

<sup>38</sup> F. F. Blicke and J. H. Burekhalter, *J. Am. Chem. Soc.* **64**, 477 (1942); S.-O. Lawesson, *Arkiv Kemi* **11**, 373 (1956); see *Chem. Abstr.* **52**, 1136 (1958).

<sup>39</sup> C. D. Hurd and H. J. Anderson, *J. Am. Chem. Soc.* **75**, 3517 (1953).

<sup>40</sup> A. Treibs and H. G. Kolm, *Ann.* **614**, 176 (1958).

<sup>41</sup> B. M. Mikhailov and V. P. Bronovitskaya, *Zh. Obshch. Khim.* **27**, 726 (1957); see *Chem. Abstr.* **51**, 16436 (1957).

<sup>42</sup> J. H. Ridd, *J. Chem. Soc.* p. 1238 (1955).

<sup>43</sup> A. Grimison and J. H. Ridd, *Proc. Chem. Soc.* p. 256 (1958).

<sup>44</sup> D. M. Brouwer, M. J. van der Vlugt, and E. Havinga, *Koninkl. Ned. Akad. Wetenschap, Proc.* **B62**, 93 (1959); see *Chem. Abstr.* **54**, 1335 (1960).

<sup>45</sup> R. Gompper and H. Rühle, *Ann.* **626**, 83 and 92 (1959).

<sup>46</sup> R. Hüttel, O. Schäfer, and G. Welzel, *Ann.* **598**, 186 and 192 (1956); R. Hüttel, H. Wagner, and P. Jochum, *ibid.* **593**, 179 (1955); R. Hüttel, O. Schäfer, and P. Jochum, *ibid.* p. 200.

<sup>47</sup> R. Hüttel and G. Welzel, *Ann.* **593**, 207 (1955).

<sup>48</sup> H. J. den Hertog and J. P. Wibaut, *Rec. Trav. Chim.* **51**, 381, 940 (1932).

<sup>49</sup> D. E. Pearson, W. W. Stargrove, J. K. T. Chow, and B. R. Suthers, *J. Org. Chem.* **26**, 789 (1961).

<sup>49a</sup> H. J. den Hertog, L. van der Does, and C. A. Landheer, *Rec. Trav. Chim.* **81**, 864 (1962).

TABLE V—continued

Heterocycle	Halogenating agent	Position of attack <sup>a</sup>	Reference
Pyrimidine	Br <sub>2</sub> (160°)	5-Bromo	50
Pyrazine	Cl <sub>2</sub> (400°)	2-Chloro	51
2. Bicyclic Nuclei			
Benzofuran	Br <sub>2</sub> in CS <sub>2</sub> : (1) KOH/C <sub>2</sub> H <sub>5</sub> OH (2) Heat	2,3-Adduct 3-Bromo 2-Bromo	16
Benzothiophen (1)	I <sub>2</sub> (HgO)	3-Iodo	52
Indole	SO <sub>2</sub> Cl <sub>2</sub>	2-Chloro	53
	KI <sub>3</sub>	3-Iodo	54
Quinoline	See Table III	5- and 8-halo	54a
	Cl <sub>2</sub> or I <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub>	5,8-Dihalo	
Isoquinoline	Br <sub>2</sub> in CCl <sub>4</sub> (C <sub>5</sub> H <sub>5</sub> N)	4-Bromo	55
	Br <sub>2</sub> (Al <sub>2</sub> Cl <sub>6</sub> )	5-Bromo 5,8-Dibromo	12
Naphthyridine (1,5)	Br <sub>2</sub> in aqueous H <sub>2</sub> SO <sub>4</sub> (135°)	3-Bromo  3,7-Dibromo	56
3. Dibenzo Derivatives			
Dibenzofuran	Br <sub>2</sub> in CS <sub>2</sub>	2-Bromo 2,8-Dibromo	57
Dibenzothiophen	Br <sub>2</sub> or NBS <sup>b</sup>	2-Bromo	58
Carbazole	Br <sub>2</sub> or 1,1-dibromo-5,5-di- methylhydantoin	3-Halo 3,6-Dihalo	59

<sup>50</sup> H. Brederick, R. Gompper, and H. Herlinger, *Ber.* **91**, 2832 (1958).<sup>51</sup> J. K. Dixon, A. A. Miller, and J. F. Bruesch, U.S. Patent 2,524,431 (1950); see *Chem. Abstr.* **45**, 2513 (1951).<sup>52</sup> R. Gaertner, *J. Am. Chem. Soc.* **74**, 4951 (1952).<sup>53</sup> G. Mazzara and A. Borgo, *Gazz. Chim. Ital.* **35**, Part II, 320 and 563 (1905).<sup>54</sup> H. Pauly and K. Gundermann, *Ber.* **41**, 3999 (1908).<sup>54a</sup> M. Kiamud-din and A. K. Choudhury, *Chem. Ind. (London)* p. 1840 (1963); M. Kiamud-din and M. E. Hague, *ibid.* p. 1753 (1964).<sup>55</sup> J. J. Eisch, Unpublished studies (1966).<sup>56</sup> W. Czuba, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **11**, No. 7, 375 (1963); see *Chem. Abstr.* **60**, 2917 (1964).<sup>57</sup> H. Gilman, G. E. Brown, W. G. Bywater, and W. H. Kirkpatrick, *J. Am. Chem. Soc.* **56**, 2473 (1934).<sup>58</sup> H. Gilman and A. L. Jacoby, *J. Org. Chem.* **3**, 108 (1938).<sup>59</sup> M. E. Fondovila, O. O. Orazi, and J. F. Salellas, *Anales Asoc. Quim. Arg.* **39**, 184 (1951); see *Chem. Abstr.* **47**, 2709 (1953).

TABLE V—continued

Heterocycle	Halogenating agent	Position of attack <sup>a</sup>	Reference
Acridine	Br <sub>2</sub> in HOAc	2-Bromo 2,7-Dibromo	31
Phenanthridine	Br <sub>2</sub> in HOAc NBS <sup>b</sup> in CCl <sub>4</sub>	2-Bromo	55 59a
Dibenzo- <i>p</i> -dioxin	Cl <sub>2</sub> or KBr—KBrO <sub>3</sub> in HOAc	2-Halo	60
Phenazine	Cl <sub>2</sub> in CCl <sub>4</sub>	1-Chloro 1,4-Dichloro	19, 61
Thianthrene	Br <sub>2</sub> in HOAc	2-Bromo	62
Phenoxathiin	Br <sub>2</sub> in CCl <sub>4</sub>	2-Bromo	63
Phenoxazine	Br <sub>2</sub> in C <sub>6</sub> H <sub>6</sub>	3-Bromo 3,7-Dibromo	64
Phenothiazine	Cl <sub>2</sub> , Br <sub>2</sub> , or HCl/H <sub>2</sub> O <sub>2</sub>	3-Halo 3,7-Dihalo	65, 66
4. Related Oxygen Derivatives			
4-Pyrone	Br <sub>2</sub> (Fe <sub>2</sub> Cl <sub>6</sub> )	3,5-Dibromo	67
2-Pyridone	Cl <sub>2</sub> , Br <sub>2</sub> , or I <sub>2</sub>	5-Halo 3,5-Dihalo	68
Pyridine- <i>N</i> -oxide	Br <sub>2</sub> and Ag <sub>2</sub> SO <sub>4</sub> in H <sub>2</sub> SO <sub>4</sub> (Br <sub>2</sub> in fuming H <sub>2</sub> SO <sub>4</sub> ) Br <sub>2</sub> and NaOAc in (CH <sub>3</sub> CO) <sub>2</sub> O	2- and 4-bromo (3-bromo) 3,5-Dibromo	69 (70) 71

<sup>59a</sup>H. Gilman and J. Eisch, *J. Am. Chem. Soc.* **77**, 6379 (1955).

<sup>60</sup>H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.* **79**, 1439 (1957).

<sup>61</sup>V. P. Chernetskii and A. I. Kiprianov, *Ukrain. Khim. Zh.* **21**, 367 (1955); see *Chem. Abstr.* **49**, 14774 (1955).

<sup>62</sup>H. Gilman and D. R. Swayampati, *J. Am. Chem. Soc.* **77**, 5944 (1955).

<sup>63</sup>C. M. Suter, J. P. McKenzie, and C. E. Marshall, *J. Am. Chem. Soc.* **58**, 717 (1936).

<sup>64</sup>H. Musso, *Ber.* **92**, 2862 (1959).

<sup>65</sup>D. S. Antonov, *Bull. Inst. Chim. Acad. Bulgare Sci.* **2**, 75 (1953); see *Chem. Abstr.* **49**, 6266 (1955).

<sup>66</sup>C. Bodea and M. Raileanu, *Ann.* **631**, 194 (1960).

<sup>67</sup>F. Feist and E. Baum, *Ber.* **38**, 3562 (1905).

<sup>68</sup>A. Binz and H. Maier-Bode, *Biochem. Z.* **257**, 351 (1933).

<sup>69</sup>H. C. van der Plas, H. J. den Hertog, M. van Ammers, and B. Haase, *Tetrahedron Letters* p. 32 (1961).

<sup>70</sup>M. Van Ammers, H. J. den Hertog, and B. Haase, *Tetrahedron* **18**, 227 (1962).

<sup>71</sup>M. Hamana and M. Yamazaki, *Chem. Pharm. Bull. (Tokyo)* **9**, 414 (1961); see *Chem. Abstr.* **55**, 24749 (1961).

TABLE V—*continued*

Heterocycle	Halogenating agent	Position of attack <sup>a</sup>	Reference
2-Quinolone	ICl in HOAc (Br <sub>2</sub> in HOAc)	3-Iodo (6-bromo)	55, 72
Quinoline- <i>N</i> -oxide	Br <sub>2</sub> (H <sub>2</sub> O at 100°)	4-Bromo	73
2-Ethoxyquinoline	Br <sub>2</sub>	4-Bromo	74
Coumarin	Br <sub>2</sub> in CS <sub>2</sub> :	3,4-Dibromo adduct	
	pyridine/heat	3-Bromo	75
Phenanthridone	Cl <sub>2</sub> , Br, or KI—KIO <sub>3</sub> in HOAc	2-Halo	76

<sup>a</sup> The heterocycle numbering is that recommended by A. M. Patterson, L. T. Capell, and D. F. Walker ["The Ring Index," 2nd ed. Am. Chem. Soc., Washington, D.C., 1960].

<sup>b</sup> NBS = *N*-bromosuccinimide.

certain empirical rules of orientation for the unsubstituted mono-heteroatomic systems. Hopefully considerable applicability of these rules to cyclic compounds containing more than one heteroatom will be possible.

(1) In neutral media the hetero ring is more reactive to halogenation than any fused benzenoid ring. But the situation is reversed with the basic pyridinoid heterocycles in highly acidic media (presence of concentrated H<sub>2</sub>SO<sub>4</sub><sup>9</sup> or Al<sub>2</sub>Cl<sub>6</sub><sup>12</sup>) [cf. Eqs. (1) and (2)].

(2) With six-membered aromatic heterocycles and their benzo derivatives substitution occurs principally beta to the heteroatom (pyridine<sup>48</sup> and coumarin<sup>75</sup> at C-3, isoquinoline at C-4<sup>55</sup>).

(3) With five-membered heterocycles principal halogenation takes place alpha to the heteroatom (thiophene at C-2<sup>38</sup>; indole is chlorinated at C-2,<sup>53</sup> but iodinated at C-3<sup>54</sup>).

(4) Elevation of the halogenation temperature tends to reverse the orientation stated by rules (2) and (3): pyridine, C-3 at 300° C and C-2 at 500°; thiophene, C-2 at 600° and C-3 at 750°. Halogenating

<sup>72</sup> E. Ochiai and T. Yokokawa, *J. Pharm. Soc. Japan* **75**, 213 (1955).

<sup>73</sup> E. Ochiai and T. Okamoto, *J. Pharm. Soc. Japan* **67**, 87 (1947).

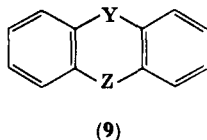
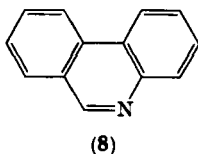
<sup>74</sup> P. Friedlander and A. Weinberg, *Ber.* **15**, 2679 (1882).

<sup>75</sup> W. H. Perkin, *Ann.* **157**, 115 (1871).

<sup>76</sup> H. Gilman and J. Eisch, *J. Am. Chem. Soc.* **79**, 5479 (1957).

agents formally classifiable as radical-promoted reagents also appear to favor  $C_\alpha$  over  $C_\beta$  for pyridinoid heterocycles.

(5) Dibenzo heterocycles tend to undergo halogenation almost always *para* with respect to the heteroatom [e.g., phenanthridine at C-2 (8)], and less frequently *ortho*. With phenazines<sup>19, 61</sup> or with benzopyridines<sup>9, 12</sup> under highly acidic conditions, the benzene ring is attacked at positions *ortho* to the hetero ring. With competing heteroatoms (Y and Z) the order of orientation control is  $N > O > S$  (9) (phenoxazine at C-3<sup>64</sup>, phenoxathiin at C-2<sup>63</sup>).



(6) In the halogenation of benzo derivatives under neutral conditions, the position *ortho* to the heteroatom is taken with lessened facility (quinoline yielding the 3,6-dibromo product, little 3,8-<sup>55</sup>; 1-substituted pyrazoles undergoing attack at C-4<sup>46</sup>).

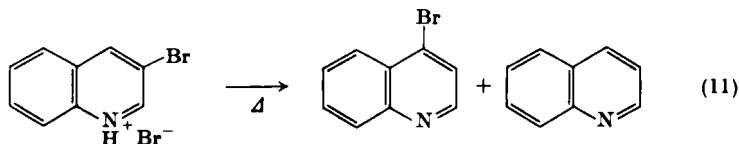
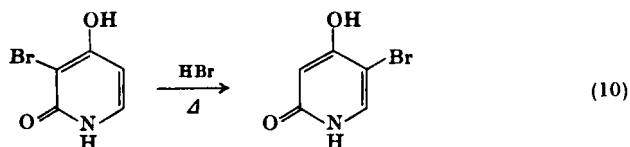
Not free from the inevitable exceptions, these rules can serve as a guide in planning preparative halogenations of novel heterocycles. In so doing, however, the possible effect of substituents on orientation must not be neglected. The behavior of oxygen derivatives of quinoline shown at the end of Table V typifies the changes in orientation possible over those observed with quinoline itself (Table III). Equally important, however, these foregoing orientation rules imply an underlying electronic unity in heterocyclic halogenation (Section III, E).

### 3. Side Reactions

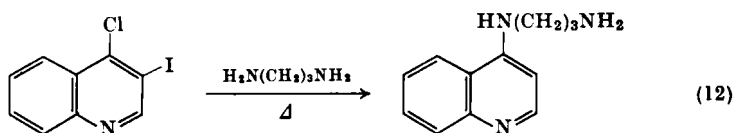
Since side reactions are often crucial in determining both the preparative utility and the mechanistic interpretation of a given process, their nature and scope demands some attention. In the first place, the observed halogenation products may be the result of rearrangement and/or dehalogenation under the reaction conditions<sup>77, 78</sup> [Eqs. (10) and (11)]:

<sup>77</sup> J. J. Eisch, *J. Org. Chem.* **27**, 4682 (1962).

<sup>78</sup> H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. Chim.* **69**, 686 (1950).



As might be anticipated, such dehalogenations are especially common in reactions of iodo derivatives<sup>79, 80</sup> [Eq. (12)]:



In a further instance 2-iodophenanthridone undergoes facile deiodination when warmed with nitric acid, although the corresponding chloro- and bromphenanthridones are nitrated smoothly at C-4.<sup>76</sup> Second, halogenating agents can cause polysubstitution on the heterocyclic system, even under conditions carefully devised for monosubstitution<sup>8, 81</sup> [Eq. (13)]. Third, the oxidation or the halogenation-oxidation of certain sensitive nuclei becomes especially bothersome in aqueous medium<sup>82</sup> [Eq. (14)]. In another instance indole is converted to indigo by iodine in aqueous sodium bicarbonate solution.<sup>82a</sup> Fourth, the side chain substitution of alkyl groups appended to less reactive rings is particularly important under conditions favoring homolytic

<sup>79</sup> A. R. Surrey and R. A. Cutler, *J. Am. Chem. Soc.* **68**, 2570 (1946).

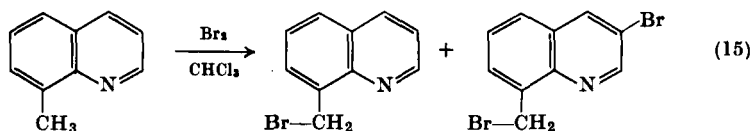
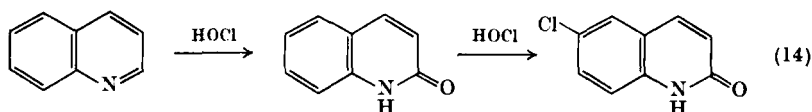
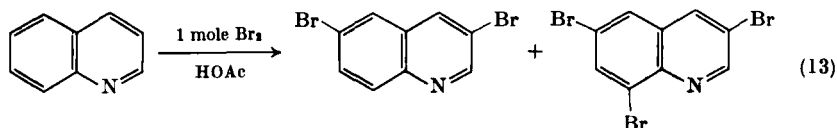
<sup>80</sup> Cf. K. W. Doak and A. H. Corwin, *J. Am. Chem. Soc.* **71**, 159 (1949), for the protodeiodination of 2- and 3-iodopyrrole derivatives.

<sup>81</sup> R. D. Brown, in "Current Trends in Heterocyclic Chemistry," Symposium (A. Albert, Chairman), Chapter 3. Butterworth, London and Washington, D.C., 1958.

<sup>82</sup> H. Decker, *J. Prakt. Chem.* [2] **45**, 47 (1892).

<sup>82a</sup> H. Pauly and K. Gundermann *Ber.*, **41**, 3999 (1908).

reactions [Eq. (15)<sup>84</sup>]. Finally, the thermal instability of certain halogenated heterocycles can cause the formation of polymeric products in high-temperature reactions (cf. behavior of 4-halopyridines).<sup>49a</sup> Such decomposition may be avoided in certain cases by use of fuming sulfuric acid.



All these undesired processes must be controlled for optimal preparative success, but the point concerning reversibility is the most vital in any mechanistic discussion. There is little validity to explaining in kinetic terms why, for example, pyridine yields the 2-bromo isomer at  $500^\circ$ ,<sup>83</sup> when its isolation may be due actually to its greater thermal or thermodynamic stability.

### III. Mechanistic Aspects of Halogenation

#### A. PRELIMINARY CLASSIFICATIONS AND FORMALISMS

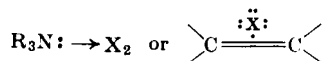
Precise mechanistic descriptions of heterocyclic halogenation are not possible with the existing experimental information. Still it appears desirable to consider what mechanistic models may be involved in such substitution processes, in an attempt both to correlate what is known and to sharpen the focus of future research. A posteriori, the most appealing reaction models are those viewing

<sup>83</sup> G. W. Wheland, "Resonance in Organic Chemistry," p. 485. Wiley, New York, 1955.

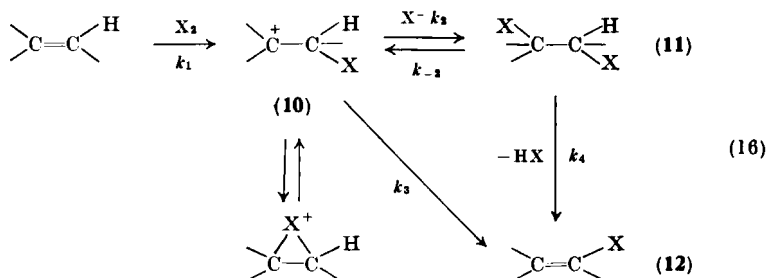
<sup>84</sup> J. Howitz and J. Philipp, *Ann.* **396**, 23 (1912).



the halogenating agents as electron-seeking electrophilic ( $\text{Br}_2$ ,  $\text{Cl}_2$ ,  $\text{H}_2\text{OCl}^+$ ) or radical ( $:\ddot{\text{Br}}\cdot$ ), while considering the heterocycles as  $n$ - or  $\pi$ -bases:



As with other aromatic substitutions, the substitution step itself can be considered to involve an approximately  $sp^3$  hybridization at the carbon atom under attack (**10**). In the idealized substitution process shown in Eq. (16), **10** may constitute either an intermediate or transition state. If proton loss ensues directly, the process is properly called a *substitution*. In other situations the intermediate **10** may become allied with a radical or an anion, leading thereby to a covalent adduct **11**. The final substituted product **12** may then be formed either by the elimination of H—Z (first H, then Z) or by the reversal to **10**, followed by proton loss. The first case is a classical example of an *addition-elimination* halogenation, where the adduct is an essential species in the process. In the second case, structure **10** is a common intermediate for both the substitution and the addition reactions. Being merely a diversion of **10**, the addition product is not essential to the substitution. In consequence of this, the isolation of adduct **11** may not mean that *addition-elimination* is the principal pathway of substitution; reversal to **10** may be faster than the elimination of H—Z ( $k_{-2}$ ,  $k_3 > k_4$ ). On the other hand, the mere failure to detect adduct **11** does not rule out an addition-elimination process, for dehydrohalogenation of adduct **11** may be much faster than its formation ( $k_4 > k_1$ ,  $k_2$ ).



In assessing the applicability of the foregoing model to a given heterocyclic halogenation, approaches such as the detection and

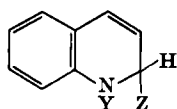
isolation of intermediates (cf. Section II, B), the kinetic behavior of these stable intermediates, possible kinetic isotope effects for deuterated heterocycles, and the kinetic response of halogenation to general base catalysis will prove especially valuable. The existing evidence on the mechanism of substitution will be treated with reference to this model.

## B. NATURE OF THE REACTING SPECIES IN THE REACTION MEDIUM

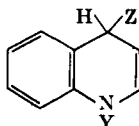
### 1. *Heterocycle Substrate*

The actual nature of the heterocyclic species undergoing halogenation may differ considerably from the parent heterocycle. The more basic nitrogen ring compounds will exist largely as their conjugate acids in powerful protonating solvents (concentrated  $\text{H}_2\text{SO}_4$ ), possibly as sulfur trioxide complexes in fuming sulfuric acid,<sup>49a</sup> or as halogen  $n$ -complexes in neutral media. Even in more weakly acidic media (acetic acid), hydrogen bonding solvation may play a role in altering the relative rates of halogenation (cf. Section III, C, 1). When acidic heterocycles of the pyrrole or imidazole type are halogenated under basic conditions, the halogenation may take place through the heterocyclic anion. Although either *N*- or *C*-halogenation may be the initial result, the *N*-halo derivative may in turn rearrange to the *C*-halo isomer.<sup>42</sup>

The previous discussion of halogen-heterocycle adducts adduced considerable evidence for the existence of complexed halogen in equilibrated systems. Various investigators have suggested the importance of such adducts both as halogenating agents themselves or as the heterocyclic substrates actually undergoing halogenative substitution. Thus 1:1 adducts of bromine with pyridine or quinoline appear to promote the halogenation of benzenoid and pyridinoid rings.<sup>1</sup> Viewed in the opposite sense, covalent addition products of heterocycles with molecular halogen, hydrogen halide, or related substances have received serious consideration as halogenation

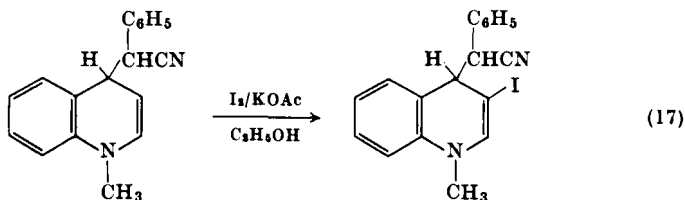


(13)

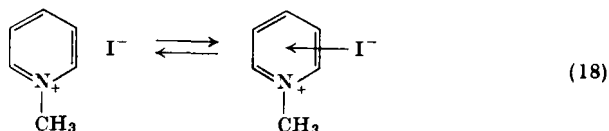


(14)

intermediates.<sup>85-88</sup> Indeed, 1,2- and 1,4-dihydroquinoline derivatives of types **13** and **14** ( $Y = \text{H}, \text{X}, \text{CN}$ ;  $Z = \text{X}, \text{OH}$ ) have been found to undergo halogenation at C-3. However, the pyridinoid ring is not always regenerated upon substitution<sup>89</sup> [Eq. (17)]:



This tends to weaken the hypothesis that halogenation at C-3 of quinoline and at C-4 of isoquinoline involves covalent intermediates of the type shown in **13** and **14**. No spectral evidence for these hypothetical adducts has as yet been obtained for the parent heterocycles and the assumption that pyridinoid methiodides may involve covalent species<sup>85</sup> has now been shown to be mistaken.<sup>26</sup> The spectral shifts seem best explained by charge-transfer ion pairs [Eq. (18)]:



## 2. Halogenating Species

The formation of other halogenating species in the reaction system depends largely on the polarity of the medium. The dissolution of bromine diquinoline perchlorate in aqueous strong acid apparently produces  $\text{HOBr}$  or  $\text{H}_2\text{OBr}^+$ . In one of the rare kinetic studies in heterocyclic halogenation the halogenation has been shown to obey the rate expression,  $-d[\text{H}_2\text{OBr}^+]/dt = k[\text{C}_9\text{H}_7\text{NH}^+][\text{H}_2\text{OBr}^+][\text{H}^+]$ .<sup>34</sup> A study of the iodination of imidazole at a  $\text{pH} = 7$  or  $> 7$  established

<sup>85</sup> M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* p. 944 (1957).

<sup>86</sup> F. Krohnke and I. Vogt, *Ber.* **90**, 2227 (1957).

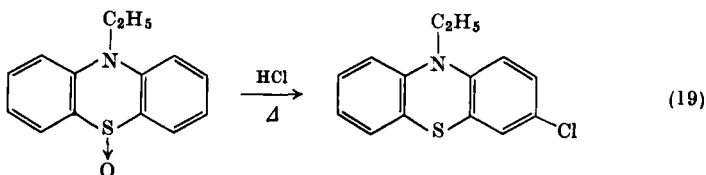
<sup>87</sup> E. E. Garcia, C. V. Greco, and I. M. Hunsberger, *J. Am. Chem. Soc.* **82**, 4430 (1960).

<sup>88</sup> R. D. Brown and R. D. Harcourt, *J. Chem. Soc.* p. 3451 (1959); *Tetrahedron* p. 23 (1960).

<sup>89</sup> N. J. Leonard and R. L. Foster, *J. Am. Chem. Soc.* **74**, 3671 (1952).

the rate law,  $v = k_1[B^-][H_2OI^+] + k_2[B^-][BHI^+]$  suggesting that the imidazole anion is being attacked by  $H_2OI^+$ , as well as by protonated *N*-iodoimidazole.<sup>42</sup>

In acidic media not as yet studied kinetically, the candidate halogenating agents can only be surmised. A solution of molecular halogen in concentrated sulfuric acid with added silver sulfate appears to generate  $X-SO_4H$  as the active species. Likewise, in aqueous acid, hypohalous acid ( $HOX$ ) and trihalide ion ( $X_3^-$ ) must be given serious consideration. Noteworthy is the generation of hypohalous acid and halogen from sulfoxides and hydrohalic acids, apparently involved, for example, in the reductive halogenation of 10-alkyl-phenothiazines<sup>6</sup> [Eq. (19)]:

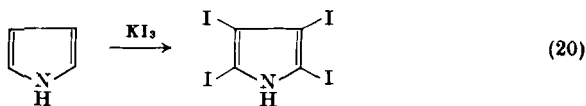


### C. ROLE OF EXPERIMENTAL CONDITIONS

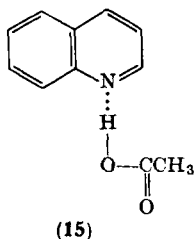
#### 1. Solvent

In addition to their decisive nature in determining the actual form of the halogenating species and heterocyclic substrate undergoing reaction, solvent, catalyst, and temperature exert great influence on the rate and selectivity of substitution. Unfortunately, the lack of rate data permits only qualitative conclusions to be drawn. As to solvents, it seems fair to say that solvents of high polarity increase the rate of heterocyclic halogenations. Recently, for example, pyridine was shown to undergo bromination faster in fuming sulfuric acid than in 90% sulfuric acid.<sup>49a</sup> Especially prominent is the tendency for nitrogen heterocycles to undergo polyhalogenation, even with limited amounts of halogen. This suggests either that the monohalo derivative is activated to further attack, compared with the unsubstituted ring, or that the parent heterocycle is deactivated compared with the substitution product. The former situation may obtain in the iodination of pyrrole by triiodide ion to yield tetraiodopyrrole.<sup>7, 40</sup> The heightened acidity of the initial iodopyrrole may aid anion formation

and hence accelerate further iodination [Eq. (20)] (cf. iodination of imidazole):

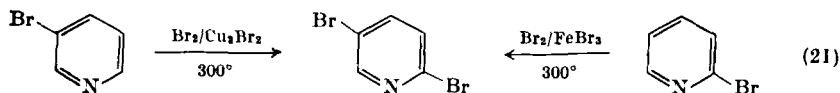


The deactivation of the parent heterocycle may be the reason why equimolar amounts of quinoline and bromine in acetic acid still give chiefly dibromo- and tribromoquinolines. The greater basicity of quinoline ( $\text{p}K_a = 4.85$ ) relative to the initially formed 3-bromoquinoline ( $\text{p}K_a = 2.51$ ) would mean the parent heterocycle would be more extensively hydrogen-bonded and, hence, deactivated by the acetic acid (15).<sup>8, 81</sup>



## 2. Promoters

The functions of the various catalysts and promoters are not altogether clear. Besides participating in the production of the actual halogenating agent, added strong acids ( $\text{H}_2\text{SO}_4$ ,  $\text{SO}_3$ ,  $\text{AlCl}_3$ ) can complex with basic centers in the heterocycle. The generation of this positive pole on the ring system leads to significant changes in the sites of halogenation (e.g., quinoline; from C-3 and C-6 to C-5 and C-8). However, the mechanisms whereby certain metal salts change the orientation in high-temperature halogenations are less readily understood. While ferric halides favor halogenation beta to the nitrogen in pyridine derivatives, cuprous halides tend to foster alpha substitution [Eq. (21)]:



Although this switch in orientation is usually explained on the basis of electrophilic attack ( $\text{Br}_2/\text{FeBr}_3$ ) vs radical attack ( $\text{Br}_2/\text{Cu}_2\text{Br}_2$ ),

evidence has not been brought forward.<sup>88</sup> Nevertheless, copper salts do form strong complexes with pyridine, and copper(II) halides, derivable from  $\text{Cu}_2\text{X}_2$ , have been shown recently to effect the halogenation of phenols.<sup>90</sup> Indeed, an electron-transfer mechanism may be involved both with phenol and with pyridine.

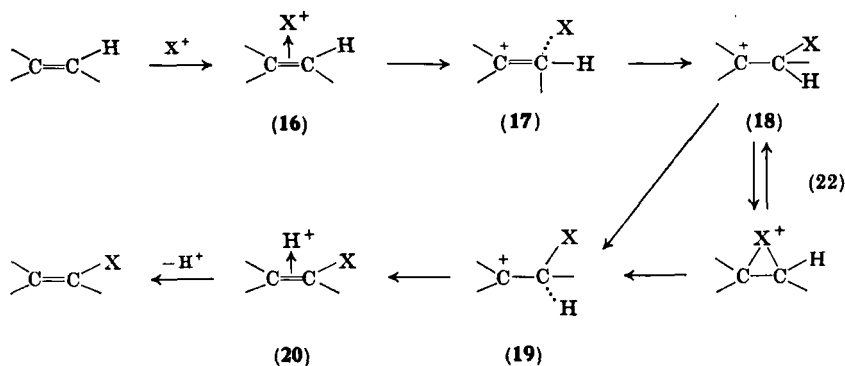
### 3. Temperature

Temperature can alter not only the rate of vapor phase halogenations but also the nature of the products [rule (4), Section II, C, 2]. Previously the uncertainty was expressed as to whether kinetic or thermodynamic factors underlie this behavior. Others have assumed, without sound evidence, that kinetic factors are decisive and that the change in orientation signifies a switch in mechanism from electrophilic to radical character. However, further speculation on this point must await equally imaginative experimentation.

## D. TENTATIVE ASSESSMENT OF TRANSITION STATE MODELS

### 1. Kinetic Consequences

Further analysis of existing models for direct electrophilic or radical substitution (cf. Section III, A for the distinction between a direct substitution and an addition-elimination pathway) would include relatively low-energy charge-transfer complexes (16 and 20) and possibly an intermediate (18) of higher energy [Eq. (22)]:



<sup>90</sup> E. M. Kosower and G.-S. Wu, *J. Org. Chem.* **28**, 633 (1963).

Moreover, the  $\pi$ -complexes (**16** and **20**) may be in equilibrium with  $n$ -complexes. With certain electrophiles bridging forms of intermediate **18**, possibly analogous to the halonium ions of olefinic systems, may be better representations. Whether bond making (transition state **17**) or bond breaking (transition state **19**) is of higher energy often may be revealed by the kinetics. Halogenations displaying a kinetic isotope effect ( $k_H/k_D > 1$ ) or showing base catalysis imply that the rate-determining step involves proton loss (T.S. **19** more energetic than T.S. **17**). Recently, the *C*-iodination of imidazole has been found to display such an isotope effect  $k_H/k_D = 4.4$ ). It should be remembered, however, that the existence of intermediate **18** and hence of a two-step process is only a postulate. In certain cases **18** might be sufficiently stable to permit verification of its presence.

## 2. Quantum Mechanical Correlations

At present, the most extensive data on heterocyclic halogenation concern the sites of substitution under different experimental conditions. In order to correlate the observed orientation with the previous transition state model, some measure is needed of how readily the various unsaturated carbon sites can provide electronic bonding to the attacking species, the electrophile,  $X^+$  (solvated) or the radical,  $:\ddot{X}\cdot$ . Several semiempirical quantum mechanical solutions to this problem have been advanced: first, reactivity indices for the isolated molecules (free valence,  $\pi$ -electron density, frontier electron density, and superdelocalizability<sup>91</sup>); and second, estimation of the energy necessary to localize an electron (or pair) at the reaction site either wholly (**18**) or partially. The latter approach adjudges configuration **18** as the better model for T.S. **17** and/or T.S. **19**, while the former view considers the starting heterocycle or a perturbed form as a reliable criterion for reactivity assessment. Since insights from aromatic substitution favor an  $sp^3$ -hybridized transition state, and since the thermic postulate would assign similar configurations to **17**, **18**, and **19**,<sup>92</sup> some type of localization calculation seems to be a more promising approach to the desired structure-reactivity correlation.

Unfortunately, the worth of such calculations is still obscured both

<sup>91</sup> A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Chapter 11. Wiley, New York, 1961.

<sup>92</sup> G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955).

by the dearth of data permitting a stringent test of theory vs. fact and by the highly approximating character of the quantum mechanical calculations employed in computing  $\pi$ -electron densities and localization energies. The most successful contribution to this field has been the calculation of localization energies for protonated aza-aromatic heterocycles and their use in predicting sites of nitration<sup>93</sup> (cf. Section III, E). In truth, the agreement between such calculated parameters and experimental findings is quite limited at present and any divergence between such calculations and the facts is not at all decisive in formulating such substitutions. A recent, discerning assessment of such theoretical approximations has also reached this disheartening conclusion.<sup>94</sup> Indeed, the successes claimed for these semiempirical calculations can also be attained by a less presumptive and qualitative resonance approach to heterocyclic halogenation. In the following section the generality of such a qualitative transition state view will be examined.

#### E. QUALITATIVE LOCALIZATION TREATMENT OF HETEROCYCLIC HALOGENATION

##### 1. *Monocyclic Systems*

In broad terms, the sites of heterocyclic halogenation follow the relative stabilities of the possible tetrahedral transition states, as assessed by a qualitative resonance treatment. For electrophilic attack the more stable transition states will be those permitting maximum positive charge dispersal, while disrupting a minimum of aromatic sextets and avoiding the positioning of the charge on electronegative heteroatoms. For five- and six-membered heterocycle transition states **21** and **22** understandably are the favored configura-



tions. Such a view unifies the substitutional behavior of furan, pyrrole, pyrazole, thiophen, pyridine, pyrimidine and 4-pyrone.

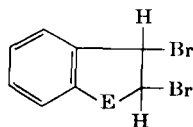
<sup>93</sup> M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* p. 2521 (1957).

<sup>94</sup> J. Ridd, in "Physical Methods of Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, Chapter 2. Academic Press, New York, 1963.



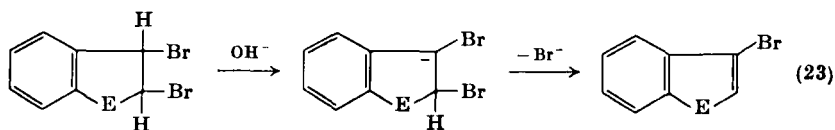
## 2. Benzo Derivatives

With benzo derivatives, competition for the halogen between benzenoid and heterocyclic rings must be considered. To explain the preference for attack in the hetero ring [rule (1), Section II, C, 2] and the resulting orientation, it may be useful to recall that disruption of aromatic conjugation becomes increasingly facile in polycyclic systems. The detection of halogen adducts with benzofuran and coumarin (**23**, E = O, O—C=O) supports the view that, in general, the hetero ring can undergo loss of aromaticity more readily than can the benzenoid ring. The orientation observed with benzo heterocycles (**23**, E = O, S, NH) suggests that diadducts or monoadduct inter-



(23)

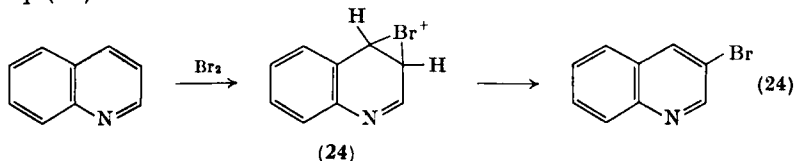
mediates may be involved. In the case of thianaphthene and indole, the intervention of diadducts of the benzofuran type may be responsible for substitution at C-3. Preferential proton abstraction from C-3 may occur because of its benzylic character. Subsequent halide ion elimination would yield the halo derivative [Eq. (23)]:



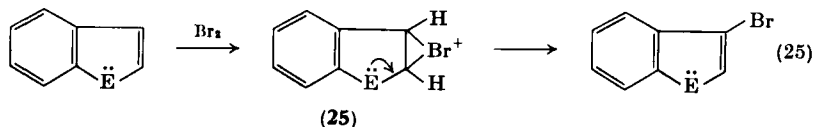
An alternative monohalogen intermediate may be implicated in the halogenation of benzo heterocycles. The widely accepted intervention of halonium ion intermediates in halogen additions to olefins<sup>95</sup> suggests that fully covalently bonded adducts of type **23** need not be formed in heterocyclic halogenation. For quinoline and isoquinoline intermediates of type **24** seem reasonable possibilities, as does **25** for thianaphthene and indole halogenations. Their formation would be favored by removing an exocyclic olefinic linkage from conjugation and their destruction to yield substitution product

<sup>95</sup> J. G. Traynham, *J. Chem. Educ.* **40**, 392 (1963).

promoted by the ease of C—Br ionization. The greater ability of C-4 in the quinoline system and C-3 in the isoquinoline system to tolerate an electron deficiency accords with the transition suggested in Eq. (24):

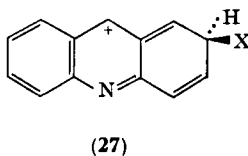
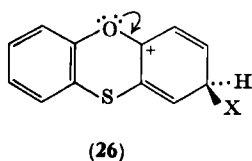


In an analogous fashion, the decomposition of the halonium ion **25** to provide the 3-halo product would be fostered by the superior ability of the adjacent S or NH to stabilize positive character at C-2 over that of phenyl to stabilize a similar deficiency at C-3 [Eq. (25)] (cf. the electrophilic orientation patterns in dibenzothiophen and in carbazole<sup>96</sup>):



### 3. Dibenzo Derivatives

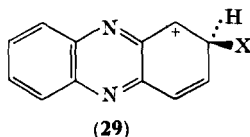
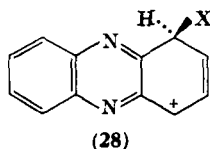
The halogenation of dibenzo derivatives of five- and six-membered heterocycles presents a rather clear orientation pattern. The preference for substitution *ortho* and *para* to atoms having available electron pairs [e.g., phenoxathiin (**26**) and carbazole] reflects the stabilization



of the transition state by such electron sources. Although similar orientation is observed with aza-aromatic systems under neutral

<sup>96</sup> See P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," p. 166. Butterworth, London and Washington, D.C., 1959.

conditions, the participation of the unshared electron pair on nitrogen cannot be invoked [acridine (27) and phenanthridine].<sup>97</sup> To a first approximation, the orthogonality of this approximately  $sp^2$ -hybridized pair with the aromatic  $\pi$ -cloud rules out such stabilization. However, for *para* and *ortho* attack at least contributing structures are avoided which place positive charge on the nitrogen atom (27). In this regard phenazine also deserves special comment. Only chlorination *ortho* to the central pyridazine ring has been reported. Although attack at either of the nonequivalent carbon atoms leads to some increase of positive charge on nitrogen, attack at C-1 involves dispersal of positive character without disrupting the quinoxaline conjugation (28 and 29).



#### 4. Systems Having Positive Poles

For basic nitrogen heterocycles in strongly acidic media ( $H_2SO_4$  or  $AlX_3$ ), halogenation will take place via a positively polarized heterocycle whose pyridinoid  $\pi$ -cloud is strongly depleted. Localization energy calculations for protonated aza-aromatic systems by simple molecular orbital theory have permitted predictions of the sites of nitration which agree satisfactorily with experimental findings<sup>93</sup> (Table VI). Halogenation of these heterocycles by the method of Derbyshire and Waters (bromine and silver sulfate in concentrated sulfuric acid) presents conditions quite comparable to those of nitration, and hence it is gratifying to note that almost equal proportions of the C-5 and C-8 isomers are obtained from both the nitration and the halogenation of quinoline. Hopefully future extension to other heterocycles will clarify the relation of this halogenation method to the many existing studies of heterocyclic nitration. It can be noted that a qualitative localization treatment, similar to that applied to neutral heterocycles, is applicable to protonated heterocycles with satisfactory results. Thus, the nitration (and, presumably, the Derbyshire-Waters halogenation) of quinoline, isoquinoline, quinoxaline, and cinnoline in the alpha positions of the benzenoid

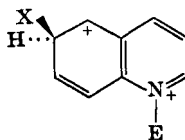
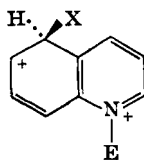
<sup>97</sup> J. Eisch and H. Gilman, *Chem. Rev.* **57**, 531-532 (1957).

ring simply reflects the deactivation of the heterocyclic ring and the greater stability of structures of type **30** over those of type **31** (cf. alpha substitution in naphthalene).

TABLE VI  
CORRELATION OF HETEROCYCLIC NITRATION WITH LOCALIZATION  
ENERGY CALCULATIONS<sup>a</sup>

Heterocycle	Positions of nitration	
	Predicted	Found (isomer ratio)
Pyridine	3	3
Quinoline	8 > 5 > 6	5 and 8 (50:50)
Isoquinoline	5 > 8 > 7	5 and 8 (90:10)
Quinoxaline	5 > 6 > 2	5
Quinazoline	8 > 6 > 5	6
Cinnoline	5 = 8 > 6	5 and 8 (54:46)
Acridine	4 > 2 > 1	2, 4, and 1 (95:?:5)
Phenanthridine	10 > 1 > 8 > 3 > 4 > 2	1, 10, 8, 3, 2, and 4 (38:31:16:9:1:4)
Benzo[ <i>f</i> ]quinoline	5 > 7 > 10 > 9	7, 10, and 9 (87:?:13)
Phenazine	1	1
Benzo( <i>c</i> )cinnoline	1 > 3	1 and 3 (83:17)

<sup>a</sup> M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 1957, 2521.



## F. UNSOLVED PROBLEMS AND VISTAS OF RESEARCH

As with most fields of chemical research, the synthetic aspects of heterocyclic halogenation have been mastered far better than have the underlying reaction mechanisms. The latter facet is intriguing not only in attaining a more intelligent control of preparative halogenation, but also in mapping the electronic response of extensively

conjugated aromatic systems to electrophilic attack. Special urgency exists for precise data on the isomer distribution and the relative reactivities of heterocycles toward various halogenating agents. Furthermore, tests of the reversibility and the role of catalysts in high-temperature halogenation deserve re-examination in the light of suggested explanations for the observed change in orientation. For halogenation in solution, the role of solvent polarity, the kinetic behavior of halogen-heterocycle adducts, the existence of kinetic isotope effects or of base catalysis, as well as the determination of halogenation rate laws, all stand in need of intensive study. The harvest of electronic insight could be great, if the laborers are not few.

#### ACKNOWLEDGMENTS

The author gratefully acknowledges fruitful discussions with Professor Jan Rocek contributing to the preparation of this chapter. This work was supported by a grant from the National Institutes of Health (GM-12329).

# The 1,2- and 1,3-Dithiolium Ions\*

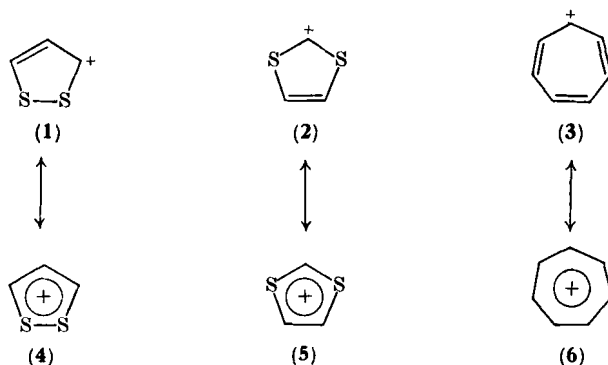
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West Germany*

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## I. Introduction

The 1,2- and 1,3-dithiolium ions (1 and 2) are unsaturated five-membered ring cations in which each of the two ring sulfur atoms can contribute a free pair of  $3p\pi$  electrons to the mesomeric bond system. Thus both systems possess a potential "aromatic" sextet, and are therefore iso- $\pi$ -electronic with the tropylium ion (3), from which they



can be formally derived by replacement of two 1,3 or 1,5  $C=C$  double bonds by two sulfur atoms.

\* Translated by Express Translation Service, London, England.

This relationship is undoubtedly responsible for much of the intensive theoretical and experimental investigation currently being carried out on these systems. The purely theoretical aspects of the relationship were recently discussed in detail by Zahradnik in a review on the "Electronic Structure of Heterocyclic Sulfur Compounds," published in Volume 5 of this series.<sup>1</sup>

Until a few years ago, however, the cations **1** and **2** had aroused little interest. In 1947 Lüttringhaus and Böttcher<sup>2</sup> recognized the products of the reaction of 1,2-dithiole-3-thiones ("trithiones") with alkyl esters of inorganic acids as 3-alkylmercapto derivatives of the 1,2-dithiolium system; these authors explained certain apparently unusual physical and chemical properties of these salts by resonance stabilization of the 1,2-dithiolium system.<sup>3</sup> Thus these "trithionium salts" were the first derivatives of the 1,2-dithiolium ion to be identified with certainty.

Hurtley and Smiles<sup>4</sup> had isolated fused-ring derivatives of **2** as early as 1926, but were understandably unable to find a satisfactory explanation for the valence relationships on the basis of the views held at that time. Wizinger and Soder,<sup>5</sup> in 1958, were the first to suggest that these "aryl-1,3-benzodithiol-1-sulfonium salts" were derivatives of the resonance-stabilized benzo-1,3-dithiolium cation.

The parent compounds **1** and **2**, however, were not synthesized until 1960 (E. Klingsberg<sup>6</sup>) and 1962 (D. Leaver *et al.*<sup>7</sup>), respectively. Most of the relevant papers on which this chapter is based were also published within the last 5 years. There is at present no universally applied nomenclature for the systems **1** and **2**, and, in addition to that used in the present article (which follows the latest rules of nomenclature used in *Chemical Abstracts*), the names "dithylium"<sup>5,8</sup> and "dithiolylum"<sup>9</sup> are also used by some groups of workers. The objections to each of the possible names have already been discussed.<sup>9</sup>

<sup>1</sup> R. Zahradnik, *Advan. Heterocyclic Chem.* **5**, 1 (1965).

<sup>2</sup> B. Böttcher and A. Lüttringhaus, *Ann.* **557**, 89 (1947).

<sup>3</sup> A. Lüttringhaus, *Angew. Chem.* **59**, 244 (1947).

<sup>4</sup> W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.* p. 1821 (1926).

<sup>5</sup> R. Wizinger and L. Soder, *Chimia (Aarau)* **12**, 79 (1958).

<sup>6</sup> E. Klingsberg, *Chem. Ind. (London)* p. 1568 (1960).

<sup>7</sup> D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.* p. 5104 (1962).

<sup>8</sup> U. Schmidt, *Ber.* **92**, 1171 (1959).

<sup>9</sup> K. A. Jensen, H. R. Baccaro, and O. Buchardt, *Acta Chem. Scand.* **17**, 163 (1963).

In some cases, however, we have retained trivial names (e.g., "trithione," "trithionium salt," "isotrithione," and "isotrithionium salt") to which there are well-founded objections, but which are widely used and appear to cause no misunderstandings.

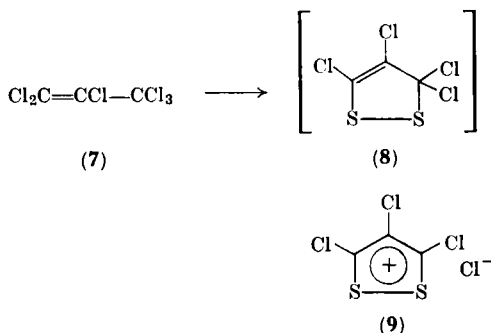
Following Zahradnik's example, we shall represent the cations **1** and **2** by the MO formulas **4** and **5**. The use of formula **4** postulating the entering of the disulfide bridge into the mesomeric system seems well-justified by recent X-ray work.

## II. The 1,2-Dithiolium Ion

### A. METHODS OF PREPARATION

#### 1. From Open-Chain Compounds

a. *From Perchloro-olefins.* When hexachloropropene (**7**) is reacted with sulfur above 160°, "tetrachloro-1,2-dithiacyclopentene" can be isolated in 65% yield.<sup>10</sup> Recent studies by Faust and Mayer.<sup>11</sup> show, however, that the chlorine in this product is not all attached by homopolar bonds (**8**), but that the substance exists as a true 1,2-dithiolium salt (**9**). Compound **9** has also been obtained (though only in small yields) by the reaction of heptachloropropane with sulfur and by the reaction of 1,1,1-trifluoro-2,3,3-trichloropropene with  $\text{Cl}_3\text{CSH}$ .<sup>12</sup>



An important point with regard to the preparation of thermally less stable halogenated dithiolium salts is that the reaction of the halogeno-olefins with sulfur proceeds at much lower temperatures in the presence of Friedel-Crafts catalysts.

<sup>10</sup> F. Boberg, *Angew. Chem.* **72**, 629 (1960); *Ann.* **679**, 109 (1964).

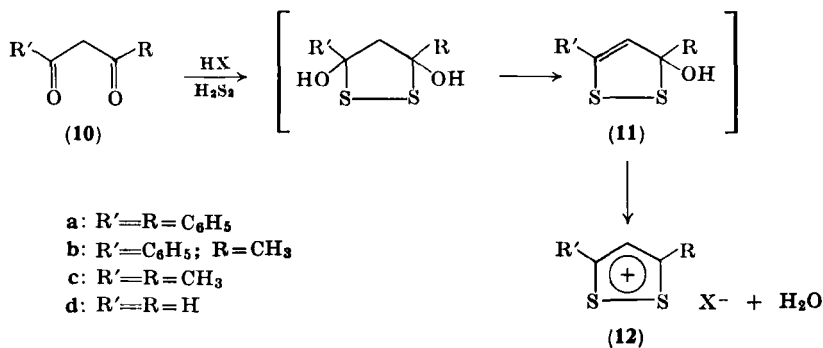
<sup>11</sup> J. Faust and R. Mayer, *Angew. Chem.* **75**, 573 (1963); *Ann.* **688**, 150 (1965).

<sup>12</sup> G. R. Schultze and F. Boberg, German Patent 1,102,174 (Cl.12q) (1959); see *Chem. Abstr.* **56**, 7326 (1962).



Hydrolysis of chlorinated dithiolium salts of this type (Section II, B, 3) yields chlorinated 1,2-dithiol-3-ones which have recently attracted attention because of their fungicidal properties.<sup>13</sup>

b. *From 1,3-Diketones and 1,3-Monothiodiketones.* According to Leaver and Robertson<sup>14a</sup> simple 1,2-dithiolium salts can be obtained by the action of  $\text{H}_2\text{S}_2$  on 1,3-diketones in HCl-saturated ether. Although no intermediates have been isolated, these reactions can probably be formally represented by Scheme 1.



SCHEME 1

The scope of this method is limited by the fact that at least one of the two substituents R and R' must be an aryl residue; this group may in fact be responsible for the relatively smooth elimination of water to form 11. Thus dibenzoylmethane (10a) and benzoylacetone (10b) give good yields of the salts 12a and 12b, which can be isolated as the perchlorates; acetylacetone (10c)<sup>7</sup> and malonic dialdehyde (10d),<sup>9</sup> on the other hand, do not undergo this reaction.

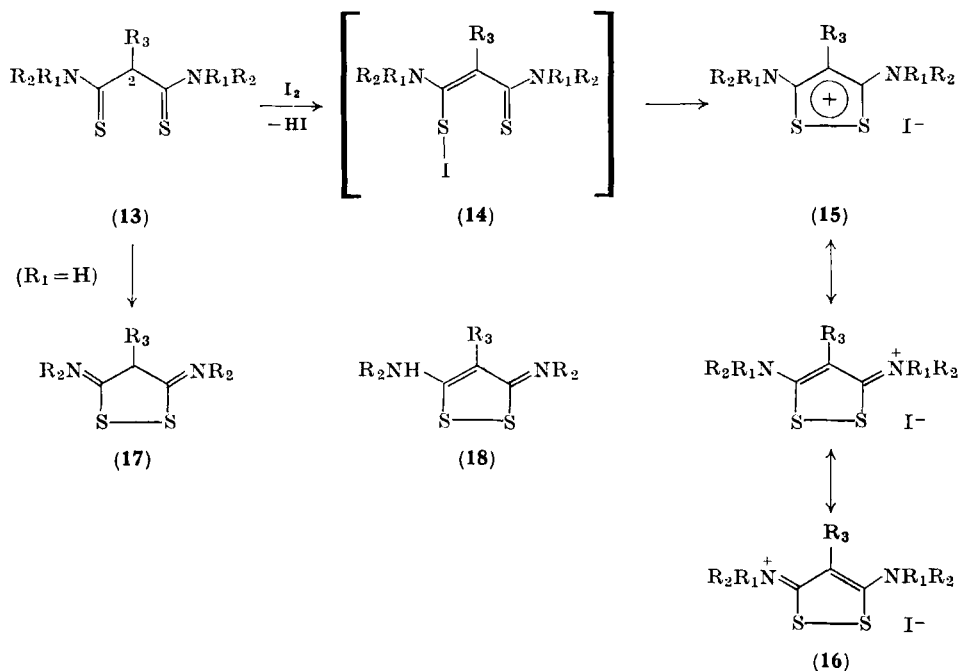
A variant of this procedure is the reaction of 1,3-diketones or 1,3-monothiodiketones with  $\text{P}_4\text{S}_{10}$  and treatment with acid.<sup>14b</sup> However, here again only 3,5-disubstituted 1,2-dithiolium salts with at least one aryl substituent can be made.

<sup>13</sup> G. R. Schultze and F. Boberg, German Patent 1,128,432 (Cl.12q) (1962); see *Chem. Abstr.* **57**, 12497 (1962).

<sup>14a</sup> D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.* p. 252 (1960).

<sup>14b</sup> H. Behringer and A. Grimm, *Ann.* **682**, 188 (1965).

c. *From 1,3-Dithiones.* Schmidt<sup>8</sup> and Jensen *et al.*<sup>9</sup> have shown that dithiomalonamides (13) (but not dithiomalonic acid) can be dehydrogenated by oxidizing agents such as I<sub>2</sub> (in ethanol), Fe(III) salts, and H<sub>2</sub>O<sub>2</sub> (in acidic media). The reaction leads to very good yields of compounds which, on the basis of their chemical behavior and their IR and UV spectra, were assumed to possess the 1,2-dithiolium structure (15). More recent X-ray (Section II, C, 2) and NMR (Section II C, 4) studies, however, while confirming the structure of these salts, indicate that their relationship to the 1,2-dithiolium system is purely formal; since the positive charge is largely localized on the two exocyclic N substituents, the salts obtained from 13 must be formulated as iminium salts (16).<sup>15</sup>



SCHEME 2

<sup>15</sup> As discussed in Section II, C, 2, the results of a two dimensional X-ray structure analysis<sup>16</sup> show that the structurally analogous thiuret ion<sup>17</sup> is also of iminium salt type.

<sup>16</sup> O. Foss and O. Tjomsland, *Acta Chem. Scand.* **12**, 1799 (1958).

<sup>17</sup> E. Fromm, *Ann.* **275**, 20 (1893).

In agreement with the postulated mechanism involving the intermediate **14** (Scheme 2), this method of preparation is confined to dithiomalonamides having at least one free hydrogen on the middle carbon atom (C-2). Dithiomalonamides with two substituents on C-2, instead of undergoing ring closure, are desulfurized by the action of the oxidizing agent. For example, 2,2-dimethyldithiomalonamide gives an almost quantitative yield of dimethylmalonamide.

The range of application of this method, as far as it has been explored at present, can be seen from Table I.

TABLE I  
"3,5-DIAMINO-1,2-DITHIOLIUM SALTS" (**15**) FROM  
DITHIOMALONAMIDES

R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Reference
H	H	H	<i>a, b</i>
H	H	C <sub>2</sub> H <sub>5</sub>	<i>b</i>
H	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<i>b</i>
H	H	NC—CH <sub>2</sub> CH <sub>2</sub>	<i>a</i>
H	H	C <sub>6</sub> H <sub>5</sub>	<i>a, b</i>
—C <sub>4</sub> H <sub>8</sub> O—		H	<i>c</i>

<sup>a</sup> U. Schmidt, *Ber.* **92**, 1171 (1959).

<sup>b</sup> K. A. Jensen, H. R. Baccaro, and O. Buchardt, *Acta Chem. Scand.* **17**, 163 (1963).

<sup>c</sup> B. Brähler, J. Reese, and R. Zimmermann, *Angew. Chem.* **74**, 468 (1962).

As the table shows, the amino substituents may contain two alkyl groups. Where R<sub>1</sub>=H and R<sub>2</sub>=C<sub>6</sub>H<sub>5</sub>, however, a product is obtained which is probably a 3,5-diimino-2,3-dithiacyclopentane (**17**).<sup>18</sup> The basicity of this compound as compared with that of the tautomeric form (**18**) is so slight that protonation does not take place under the reaction conditions used, although a stable, sparingly soluble molecular compound is formed with picric acid.

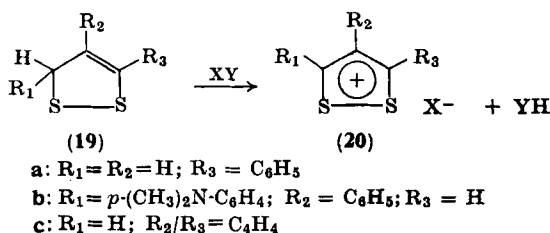
The ability to undergo oxidative ring closure [(**13**)→(**15**)] places the dithiomalonamides in a special position among the dithiodicarboxylic acid diamides: in some way, which is not yet quite clear,

<sup>18</sup> A. Reissert and A. Moré, *Ber.* **39**, 3298 (1906).

the homologous  $\alpha,\omega$ -dithioamides are partially desulfurized and oxidized to open-chain thioamide *S*-oxides.<sup>19</sup>

## 2. From 1,2-Dithiole Derivatives

a. *Oxidation.* The obvious method of preparing relatively stable organic cations is by hydride abstraction from suitable starting materials. This method, however, which is frequently successful in hydrocarbon chemistry (particularly in the tropilidene series<sup>20</sup>) and in the chemistry of other "thiaaromatics,"<sup>4, 21, 22</sup> has proved useful for only a few 1,2-dithiole derivatives of the general type **19**.



The factors that limit the scope of this method undoubtedly include the thermal instability of the simple 1,2-dithioles (all investigations known to the authors indicate that 1,2-dithiole is incapable of existing) and the extreme reactivity of these leuco bases.

Thus the leuco bases expected from the reaction of aryl-substituted 1,2-dithiolium salts with tertiary aromatic amines can only occasionally be obtained as such (e.g., **19b**). The 1,2-dithiole derivatives (**19**) generally suffer rapid loss of hydride ion by the unreacted 1,2-dithiolium salt or by added oxidizing agent.<sup>23</sup> It has recently been shown<sup>24</sup> that 1,2-dithiole derivatives can be isolated only if the ring is stabilized by several aryl substituents. The compounds are then reasonably stable, and can be reconverted into the starting salts by the action of strong acids (Section II, B, 3).

1,2-Dithioles (**19**) have also been postulated as intermediates

<sup>19</sup> W. Walter and J. Curts, *Ann.* **649**, 88 (1961).

<sup>20</sup> T. Nozoe, *Progr. Org. Chem.* **5**, 132 (1961).

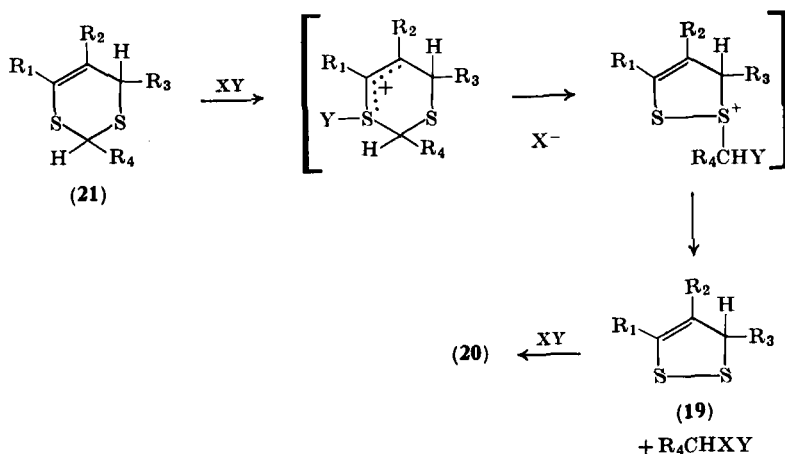
<sup>21</sup> A. Lüttringhaus, N. Engelhard, and A. Kolb, *Ann.* **654**, 189 (1962).

<sup>22</sup> J. Degani, R. Fochi, and C. Vincenzi, *Tetrahedron Letters* **18**, 1167 (1963).

<sup>23</sup> E. Klingsberg and A. M. Schreiber, *J. Am. Chem. Soc.* **84**, 2941 (1962).

<sup>24</sup> D. Leaver, D. M. McKinnon, and W. A. H. Robertson, *J. Chem. Soc.* p. 32 (1965).

(which cannot, however, be isolated) in the oxidative contraction of the 1,3-dithiacyclohexene ring [(21)→(20)].<sup>25</sup>



SCHEME 3

Suitable oxidizing agents include bromine (in benzene) and sulfonyl chloride (in ether/glacial acetic acid). The scope of this method has not yet been fully explored, and appears to be capable of further modification and expansion. Though laborious in comparison with other routes, it makes possible the preparation of certain 1,2-dithiolium salts that cannot be obtained, for example, by the extremely simple Klingsberg method (Section II, A, 2,b).

Thus the benzo-1,2-dithiolium ion (20c), which is of interest for comparative studies with the iso- $\pi$ -electronic naphthalene, the benzotropylium ion,<sup>25a</sup> the 1-thianaphthalinium ion,<sup>26-30</sup> and the 2-thianaphthalinium ion,<sup>27</sup> can be obtained in good yield via the cyclic mercaptal (21) ( $R_1/R_2 = C_6H_4$ ;  $R_3 = H$ ).<sup>25</sup>

In agreement with the reaction mechanism outlined in Scheme 3 (the first step of which resembles the much-studied formation of

<sup>25</sup> A. Lüttringhaus, M. Mohr, and N. Engelhard, *Ann.* **661**, 84 (1963).

<sup>25a</sup> D. Meuche, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta* **41**, 57 (1958).

<sup>26</sup> A. Lüttringhaus and N. Engelhard, *Naturwiss.* **44**, 584 (1957).

<sup>27</sup> A. Lüttringhaus and N. Engelhard, *Ber.* **93**, 1525 (1960).

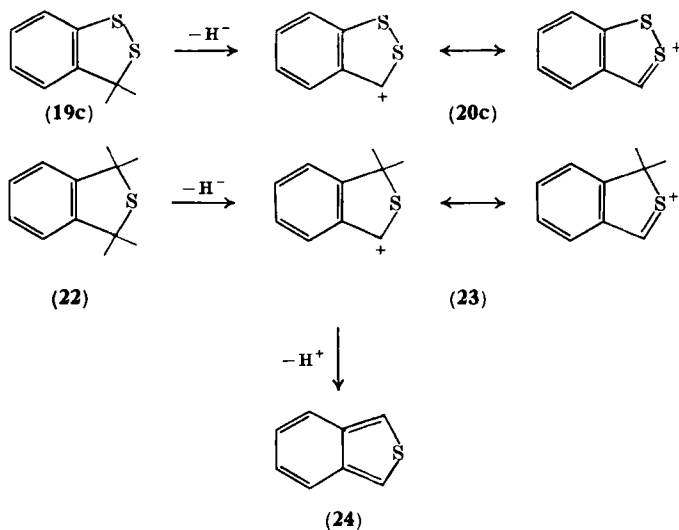
<sup>28</sup> N. Engelhard and A. Kolb, *Angew. Chem.* **73**, 218 (1961).

<sup>29</sup> A. Lüttringhaus, N. Engelhard, and A. Kolb, *Ann.* **654**, 189 (1962).

<sup>30</sup> N. Engelhard and A. Kolb, *Angew. Chem.* **75**, 1117 (1963).

disulfides from mercaptals<sup>31-33</sup>), the oxidation of 1,2-dithiahydrindene (**19c**) (which exists for only a short time in the pure form at 20°, <sup>33a</sup> but which is stable as a 0.5 *M* solution in CS<sub>2</sub>) proceeds in good yield,<sup>34-35</sup> even under mild conditions, with the reagents used to convert **21** into **20**, as well as with other hydride acceptors (trityl perchlorate; PCl<sub>5</sub>/HClO<sub>4</sub>) used in the tropilidene/tropylium ion system.<sup>20</sup>

It may be worth noting at this point that 2-thiahydrindene (**22**) cannot be oxidized to the cation (**23**) under these conditions.<sup>34</sup> Although it is not yet certain what actually does happen when trityl salts react with **22** [the deeply colored products may result from further reaction of 3,4-benzothiophene (**24**)<sup>36</sup>], **23** cannot even be detected as the perchlorate, far less isolated.



<sup>31</sup> F. Weygand, H. Ziemann, and H. J. Bestmann, *Ber.* **91**, 2534 (1958).

<sup>32</sup> R. Kuhn, W. Baschang-Bister, and W. Däfeldecker, *Ann.* **641**, 160 (1961).

<sup>33</sup> K. D. Gundermann, *Angew. Chem.* **75**, 1194 (1963).

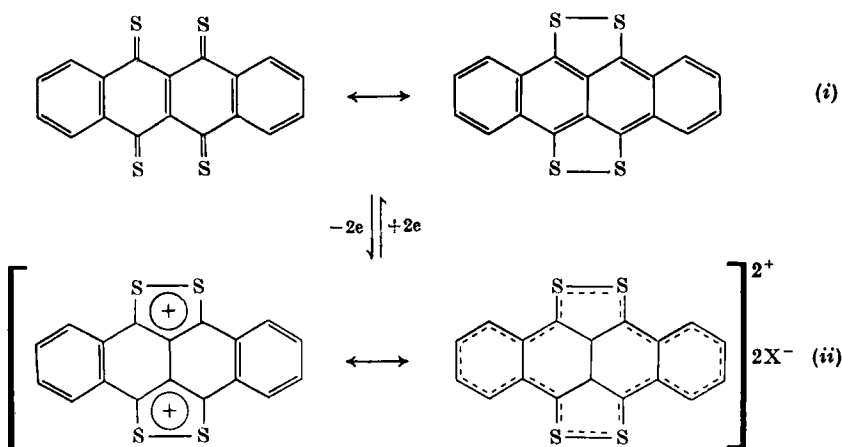
<sup>33a</sup> A. Lüttringhaus and K. Hägele, *Angew. Chem.* **67**, 304<sup>1</sup> (1955).

<sup>34</sup> A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Ber.* (in press).

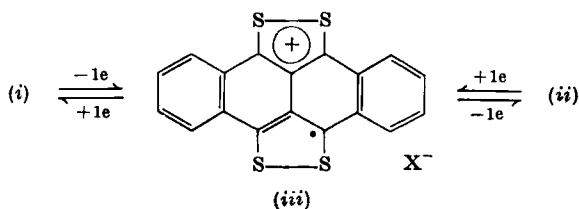
<sup>35</sup> The stereochemical implications of this ring-contraction have recently been studied in the 1,3-dithian series: K. J. S. Beer, D. Harris, and D. J. Royall, *Tetrahedron Letters* **24**, 1531 (1964).

<sup>36</sup> R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.* **20**, 244 (1963).

The benzylcarbonium-sulfonium salt (**23**) evidently lacks the stability and integrity of the benzo-1,2-dithiolium salt (**20c**), which is also a benzylcarbonium-sulfonium salt, as shown by two of its canonical structures. Thus the benzylcarbonium ion character common to **20c** and **23**, with additional stabilization by the adjacent sulfur atom, is not sufficient to explain the stability of the ion **20c**. A very attractive though not yet fully explained example is the yellow-orange dipositive cation obtained by a two-electron oxidation (e.g., by  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{Cl}_2$ , etc.) of the dark-green tetrathiotetracene (*i*)<sup>37</sup> which at least formally can be looked on as a bis-1,2-dithiolium system. In agreement with a delocalization of the charge as formulated in (*ii*) are the NMR data.<sup>38</sup>



(*ii*) is easily reduced, e.g., by  $\text{TiCl}_3$ , to the red-violet ion radical (*iii*), obtainable also by one-electron oxidation of (*i*) or by synproportionation of (*i*) plus (*ii*).

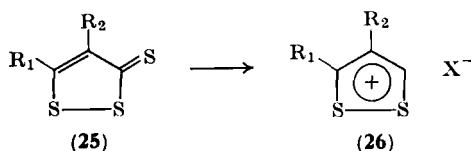


<sup>37</sup> C. Marschall, *Bull. Soc. Chim. France* p. 147 (1952).

<sup>38</sup> A. Lüttringhaus, E. Futterer, and H. Prinzbach, To be published.

b. *Reduction.* The 1,2-dithiolium ion can be formally regarded as a lower oxidation state of "trithione." In analogy with the preparation of thiazoles<sup>39</sup> and imidazoles<sup>40, 41</sup> from the corresponding 2-thione derivatives,<sup>42</sup> the reduction of **25** to **26** with 40% peracetic acid (in acetone) generally proceeds in good to very good yields, the thione sulfur being oxidized to the sulfate anion.

Useful variants of this Klingsberg method<sup>43</sup> are oxidation with 30% H<sub>2</sub>O<sub>2</sub> in glacial acetic acid<sup>7</sup> or in CH<sub>3</sub>OH/H<sub>2</sub>SO<sub>4</sub>.<sup>19</sup> Oxidation with chlorine in glacial acetic acid is more complex and gives only very modest yields.<sup>44</sup>



Although the dithiolium salts (**26**) are stable for some time towards the oxidizing agents used (as well as towards nitric acid, for example) another important factor that contributes to the high yields of the Klingsberg process is the fact that the dithiolium salt is only very slightly soluble in acetone, and is therefore withdrawn from the further action of the oxidizing agent. This method can also be used to prepare the acetone-soluble 3,4-diphenyl-1,2-dithiolium sulfate, however, provided that the salt is sufficiently rapidly isolated as the insoluble perchlorate.<sup>45</sup> The prolonged action of peracids leads to complex secondary reactions.<sup>46</sup> Our present knowledge of the sensitivity of the salts (**26**) towards alkalies explains the results of earlier studies on "trithiones," in which oxidation in an alkaline medium led to the complete destruction of the ring system.<sup>2, 47a</sup>

<sup>39</sup> E. R. Buchmann, A. O. Reims, and H. Sargent, *J. Org. Chem.* **6**, 764 (1941).

<sup>40</sup> I. E. Balaban and H. King, *J. Chem. Soc.* p. 1858 (1927).

<sup>41</sup> T. O. Norris and R. L. McKee, *J. Am. Chem. Soc.* **77**, 1056 (1955).

<sup>42</sup> A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **2**, 61 (1963).

<sup>43</sup> E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961); see also U.S. Patent 3,158,621 (1962); see *Chem. Abstr.* **62**, 10575 (1965).

<sup>44</sup> H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. France* p. 1167 (1963).

<sup>45</sup> E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

<sup>46</sup> A. Lüttringhaus and W. Cleve, *Ann.* **575**, 112 (1952).

<sup>47a</sup> F. Bauer, *Chem. Ztg.* **75**, 3 (1951).



Whereas "trithiones" (some of them at least) were until recently obtainable only at great preparative cost, a number of simple and very productive syntheses have been developed in the past few years.<sup>47b</sup> The oxidative elimination of the thione sulfur from the "trithiones" has therefore become the most important method of synthesizing 1,2-dithiolium salts (Table II). The substituents R<sub>1</sub> and R<sub>2</sub> may be

TABLE II  
1,2-DITHIOLIUM SALTS (26) BY REDUCTION OF "TRITHIONES"

R <sub>1</sub>	R <sub>2</sub>	X	Yield (%)	Reference
H	H	I, ClO <sub>4</sub>	50	a, b
C <sub>6</sub> H <sub>5</sub>	H	HSO <sub>4</sub>	65-70	c
		I		c
		ClO <sub>4</sub> , Br		c, d
C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	HSO <sub>4</sub>	80-100	e, f
		Br		g
C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	HSO <sub>4</sub>	94	c
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,4)	H	HSO <sub>4</sub> , Br	90	d
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,5)	H	HSO <sub>4</sub> , Br	90	d
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (3,4)	H	HSO <sub>4</sub> , Br	100	d
C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (3)	H	HSO <sub>4</sub>	70	c
C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	Br	—	c
H	C <sub>6</sub> H <sub>5</sub>	HSO <sub>4</sub> , Br, SCN, ClO <sub>4</sub>	85	c
H	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	HSO <sub>4</sub>	66	c
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub>	36.5	d

<sup>a</sup> E. Klingsberg, *Chem. Ind. (London)* p. 1568 (1960).

<sup>b</sup> D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.* p. 5104 (1962).

<sup>c</sup> E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961).

<sup>d</sup> E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

<sup>e</sup> W. Walter and J. Curts, *Ann.* **649**, 88 (1961).

<sup>f</sup> H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. France* p. 1167 (1963).

<sup>g</sup> A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Tetrahedron Letters* **19**, 1209 (1963).

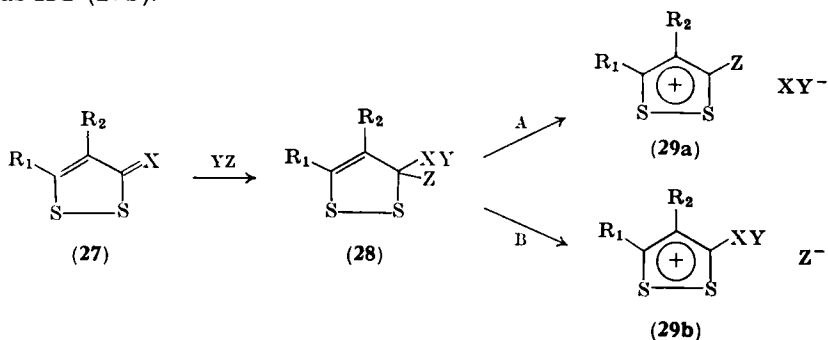
varied, but there will always be a hydrogen atom in position 3. The possibility of extending this method to the preparation of alkyl-substituted 1,2-dithiolium salts, which may be sensitive towards

<sup>47b</sup> P. S. Landis, *Chem. Rev.* **65**, 237 (1965); J. Faust and R. Mayer, *J. Prakt. Chem.* **26**, 340 (1964); R. Mayer, P. Wittig, J. Fabian, and R. Heitmüller, *Ber.* **97**, 654 (1964).

oxidation, does not yet appear to have been investigated with sufficient thoroughness.

c. *Exchange of Substituents.* This section deals with reactions in which compounds of the type **27** ( $X \neq 2H$ ) are converted to 1,2-dithiolium salts (**29**) with a substituent in position 3. Following our formal classification, this can be regarded simply as a substituent exchange on the heterocyclic ring, the oxidation state of which remains unaltered.

According to whether the intermediate **28** dissociates by path A or by path B, the product is a 1,2-dithiolium salt in which the original exocyclic residue X has been replaced by Z (**29a**) or has been retained as XY (**29b**).



The dissociation of **28** by path A is exemplified by the reactions of the 1,2-dithiol-3-ones (**30a**) ("Baumann-Fromm disulfides"<sup>48</sup>) and of the "trithiones" (**30b**) with halogens.

The exocyclic chalcogen in **30** is displaced by direct chlorination,<sup>49,50</sup> or preferably by the action of oxalyl chloride.<sup>11</sup> The products are again (Section II, A, 1, a) true 3-chloro-1,2-dithiolium salts (**32**), contrary to the original formulation, which involved two covalent C-Cl bonds (**31**). The range of application of this method and the yields obtained can be seen from Table III.

The same result, i.e., substitution in position 3, is obtained by substituent exchange between **30** and tertiary amines in the presence of suitable Lewis acids, such as Cl<sub>3</sub>CSCl or POCl<sub>3</sub>; the product is **34**. As we shall show later, "trithiones" react smoothly with esters of

<sup>48</sup> E. Baumann and E. Fromm, *Ber.* **30**, 11 (1897).

<sup>49</sup> R. S. Spindt, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.* **73**, 3693 (1951).

<sup>50</sup> P. S. Landis and L. A. Hamilton, *J. Org. Chem.* **25**, 1742 (1960).

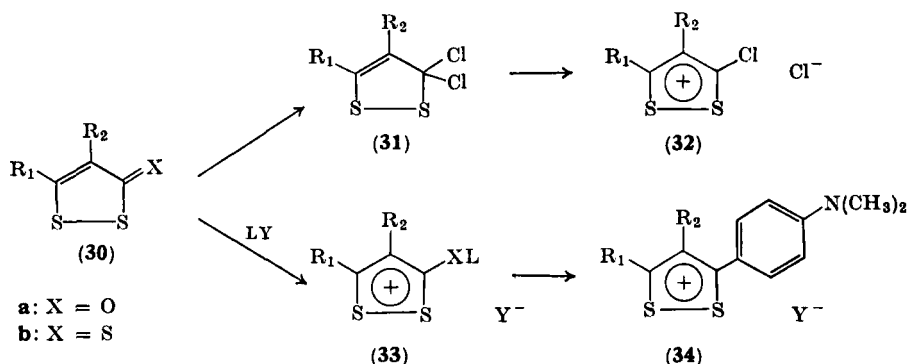


TABLE III

CHLORO-SUBSTITUTED 1,2-DITHIOLIUM SALTS (32) FROM  
"BAUMANN-FROMM DISULFIDES" AND "TRITHIONES"

$R_1$	$R_2$	Yield (%)	Reference
$C_6H_5$	H	80	a
H	$CH_3$	—	b
$CH_3$	$(CH_3)_3C$	68	b
H	$(CH_3)_3C-CH_2$	—	b
$(CH_3)_3C$	$(CH_3)_3C-CH_2$	89	c
Cl	$CH_3$	—	d
Cl, Br	$C_6H_5$	—	d, e, f
Cl	$C_6H_4-CH_3$ (4)	—	d, f
Cl	$C_6H_4-C_6H_5$ (4)	—	d
Cl	Cl	—	f

<sup>a</sup> J. Faust and R. Mayer, *Angew. Chem.* **75**, 573 (1963).

<sup>b</sup> R. S. Spindt, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.* **73**, 3693 (1951).

<sup>c</sup> P. S. Landis and L. A. Hamilton, *J. Org. Chem.* **25**, 1742 (1960).

<sup>d</sup> Hercules Powder Co., British Patent 900,805 (Cl. C07d, A01n) (1962); see *Chem. Abstr.* **61**, 3113 (1964).

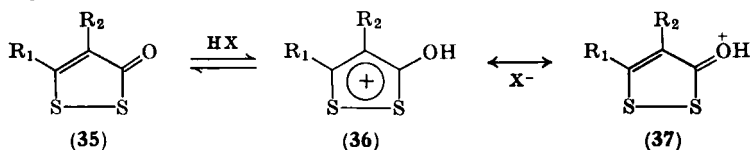
<sup>e</sup> L. E. Carosino, U.S. Patent 3,109,772 (Cl. 167-33) (1963); see *Chem. Abstr.* **60**, 2933 (1964).

<sup>f</sup> J. Faust and R. Mayer, *Ann.* **688**, 150 (1965).

inorganic acids to form "trithionium salts" (33b); the above reactions are therefore simply modifications of the long familiar nucleophilic substitution of "trithionium salts" (Section II, B, 3).

The literature contains many more examples of the preparation of 3-substituted 1,2-dithiolium salts of the type 29b, in which the exocyclic residue of 27 may be O, S, NR, or CRR.

As we have pointed out earlier, the 1,2-dithiol-3-ones (**35**) cannot apparently be alkylated with dimethyl sulfate or methyl iodide (as far as we know, more efficient alkylating agents such as trialkyloxonium fluoroborates<sup>51</sup> have not so far been used); protonation does occur, however, in media of high protonating activity.<sup>52</sup> The extent to which the conjugate acids of **35** can be regarded as 3-hydroxy-1,2-dithiolium salts (**36**) is not yet known. Nuclear resonance studies indicate that the dithiolium limiting form (**36**) makes only a minor contribution to the resonance hybrid, and that the form that corresponds most closely to the true electron distribution is **37**<sup>53</sup> (Section II, C, 4).



This is understandable, since the stabilizing influence of oxygen on an adjacent positive center by means of a free electron pair is stronger than that of bivalent sulfur.<sup>54</sup>

Similar restrictions also apply in the case of the saltlike products obtained by the action of electrophilic reagents on the relatively more basic "trithiones" (**38**).

A characteristic property of the "trithiones" is that they dissolve in medium to strong acids with brightening of their colors.<sup>55, 55a</sup>

<sup>51</sup> H. Meerwein, W. Florian, W. Schön, and G. Stopp, *Ann.* **641**, 1 (1961).

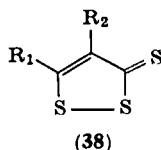
<sup>52</sup> E. Futterer, Diplomarbeit, Freiburg-im-Breisgau (1963).

<sup>53</sup> A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Tetrahedron Letters* **19**, 1209 (1963).

<sup>54</sup> C. C. Price and S. Oae, "Sulfur Bonding," Chapter 6. Ronald Press, New York, 1962.

<sup>55</sup> W. Cleve, Dissertation, Halle (1950).

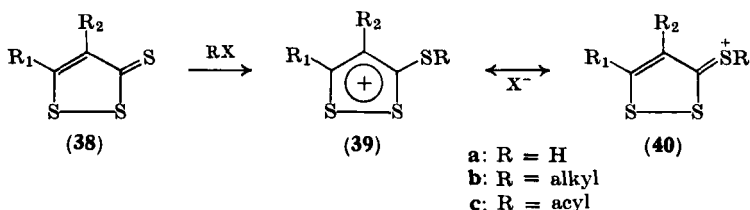
<sup>55a</sup> The base strength of some "trithiones"—as measured by  $H_0$  (half-protonation)—has been determined spectrophotometrically in aqueous sulfuric acid (25.0°) by R. Mayer *et al.* (work to be published).



R <sub>1</sub>	R <sub>2</sub>	-H <sub>0</sub>
H	H	3.97
CH <sub>3</sub>	CH <sub>3</sub>	3.41
—(CH <sub>2</sub> ) <sub>3</sub> —		3.53
—(CH <sub>2</sub> ) <sub>4</sub> —		3.42
—(CH <sub>2</sub> ) <sub>5</sub> —		3.32
H	C <sub>6</sub> H <sub>5</sub>	4.02
C <sub>6</sub> H <sub>5</sub>	H	3.68
—C <sub>4</sub> H <sub>4</sub> —		4.83

It appears from UV spectrophotometric data, and above all from recent NMR data, that, as expected, the contribution of the 1,2-dithiolium form (**39a**) to the resonance hybrid of the conjugate acids of **38** is greater than in the case of the 3-hydroxy and 3-amino analogs (**36** and **48**). Even here, however, there is only limited justification for formulating these conjugate acids as true 3-mercapto-1,2-dithiolium salts (**39a**).<sup>56</sup> A very similar electron distribution occurs in the 3-alkylmercapto-1,2-dithiolium ("trithionium") salts (**39b**), which are obtained in good to very good yields under very mild conditions by the action of dimethyl sulfate or of methyl or higher alkyl halides on **38**.<sup>2, 57, 58</sup>

In contrast to these generally stable 3-alkylmercapto-1,2-dithiolium salts, the 3-acyl derivatives (**39c**), which have only recently been synthesized by R. Mayer and his co-workers, are very unstable and highly sensitive towards hydrolysis.<sup>11, 59</sup>



The numerous addition compounds of the "trithiones" with salts of heavy metals (Cu, Ag, Au, Zn, Cd, Hg, Mn, Fe, Co, Ni, Al, Sn, Pb, Sb, Bi, Pt, Pd<sup>2</sup>,<sup>50, 60-62</sup>), most of which are sparingly soluble and characteristically colored, have also been formulated by various authors as 1,2-dithiolium salts.

The stoichiometric compositions of these complexes differ according to the nature of the metal cation. They are mostly 1:1 complexes, but  $\text{SnCl}_4$ ,<sup>63, 64</sup> for example, is capable of complexing with two equiva-

<sup>56</sup> J. Teste and N. Lozac'h, *Bull. Soc. Chim. France* p. 437 (1955).

<sup>57</sup> B. Böttcher and F. Bauer, *Ann.* **568**, 227 (1950).

<sup>58</sup> A. Lüttringhaus and U. Schmidt, *Chem. Ztg.* **77**, 135 (1953).

<sup>59</sup> R. Mayer and H. Hartmann, *Ber.* **97**, 1886 (1964).

<sup>60</sup> M. Lozac'h, *Bull. Soc. Chim. France* p. 840 (1949).

<sup>61</sup> N. G. Voronkov, A. S. Broun, and G. B. Karpenko, *Zh. Obshch. Khim.* **19**, 1927 (1949); see *Chem. Abstr.* **44**, 1955 (1950); M. G. Voronkov and F. P. Tsiper, *Zh. Anal. Khim.* **6**, 331 (1951); see *Chem. Abstr.* **46**, 2953 (1952).

<sup>62</sup> A. Lüttringhaus, R. Cordes, and U. Schmidt, *Angew. Chem.* **67**, 275 (1955).

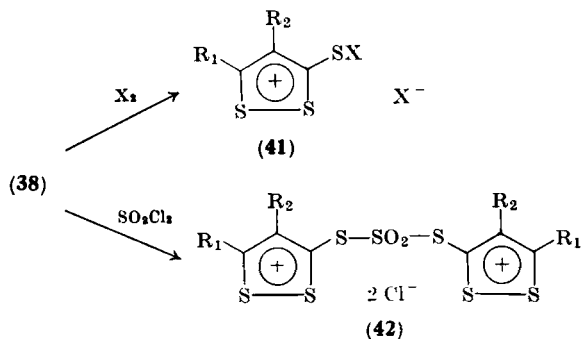
<sup>63</sup> N. Lozac'h and O. Gaudin, *Compt. Rend.* **225**, 1162 (1947).

<sup>64</sup> Y. Mollier and N. Lozac'h, *Bull. Soc. Chim. France* p. 1076 (1952).

lents of "trithione." The Hg adducts are of particular preparative interest; the free "trithiones" are regenerated on addition of reagents that bind mercury, so that these adducts can be used to advantage in the separation and purification of "trithiones" from the frequently complex reaction mixtures.

Although it is probable, in view of the chemical properties of the "trithiones," that the metal cation attacks at the exocyclic thione sulfur, all our ideas regarding the actual bonding in these complexes are at present largely speculative.<sup>65</sup> In particular, no convincing arguments have as yet been advanced in favor of the widely accepted saltlike character that is of interest here.

The same uncertainty exists with regard to the bonding in the addition products of "trithiones" with  $\text{Cl}_2$ ,  $\text{Br}_2$ , and  $\text{I}_2$ ,<sup>62, 64</sup> and with the acid chlorides  $\text{SO}_2\text{Cl}_2$ ,  $\text{SOCl}_2$ ,<sup>63, 64</sup> and  $\text{S}_2\text{Cl}_2$ .<sup>66</sup> The relatively high melting points of all these crystalline adducts, many of which decompose very readily, but which have very definite compositions, can be taken as evidence for the 1,2-dithiolium salt structures (e.g., **41** or **42**); however, physical measurements that could conclusively establish the saltlike character have not so far been carried out.



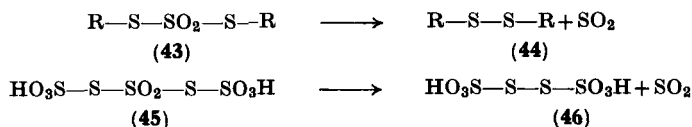
Nevertheless, the dithiolium structures (42) postulated by French workers for the products of the reaction of "trithiones" with sulfonyl chloride can be fairly certainly ruled out. Branched polysulfane derivatives of this kind (the sulfone O atoms can be regarded as quasi-branches<sup>67</sup>) are extremely unstable. They decompose rapidly

<sup>65</sup> A. Lüttringhaus and H. Götze, *Angew. Chem.* **64**, 661 (1952).

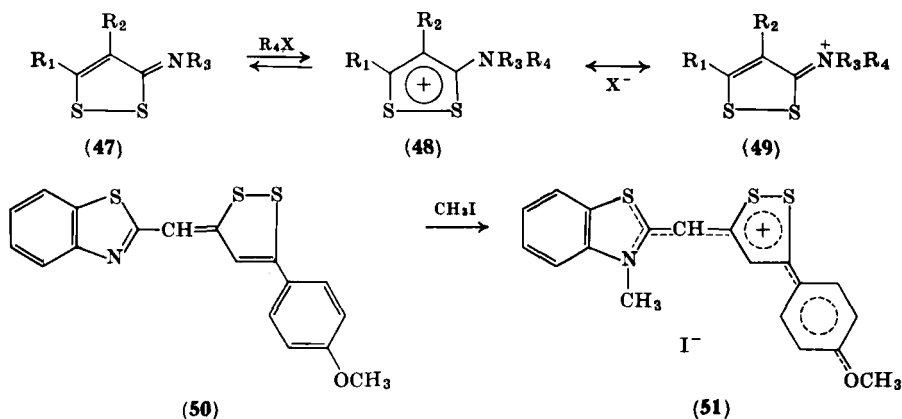
<sup>66</sup> H. Trefzger, Dissertation, Freiburg-im-Breisgau (1955).

<sup>67</sup> O. Foss, in "Organic Sulfur Compounds" (N. Kharash, ed.), Chapter 8. Pergamon Press, Oxford, 1961.

with elimination of  $\text{SO}_2$  to form the straight-chain disulfanes, just as the analogous products **43** and **45**, obtained from the reaction of  $\text{SO}_2\text{Cl}_2$  with mercaptans and with thiosulfuric acid, respectively, decompose into **44** and **46**.<sup>68</sup>



Like the "trithiones," the 1,2-dithiolimines (**47**) (the Schiff's bases of the "Baumann-Fromm disulfides") can be readily protonated and alkylated.<sup>69</sup> Although the products can again be formally described as 1,2-dithiolium derivatives having the limiting formula **48**, it is evident from X-ray and NMR measurements on the 3,5-diamino salts (**15**) and on the 3-hydroxy or 3-alkylmercapto derivatives (**36** and **39**) that the true charge distribution corresponds much more closely to the iminium limiting structure (**49**). The same is true of the cyanine dye salts (**51**) obtained by methylation of compounds of type **50**.<sup>70</sup> This reaction involves the alkylation of a vinylogous Schiff's base of a "Baumann-Fromm disulfide." The analogy with the "trithiones" extends to the addition of salts of heavy metals<sup>69</sup>; thus **47** readily adds on  $\text{HgCl}_2$  to form a product whose structure is



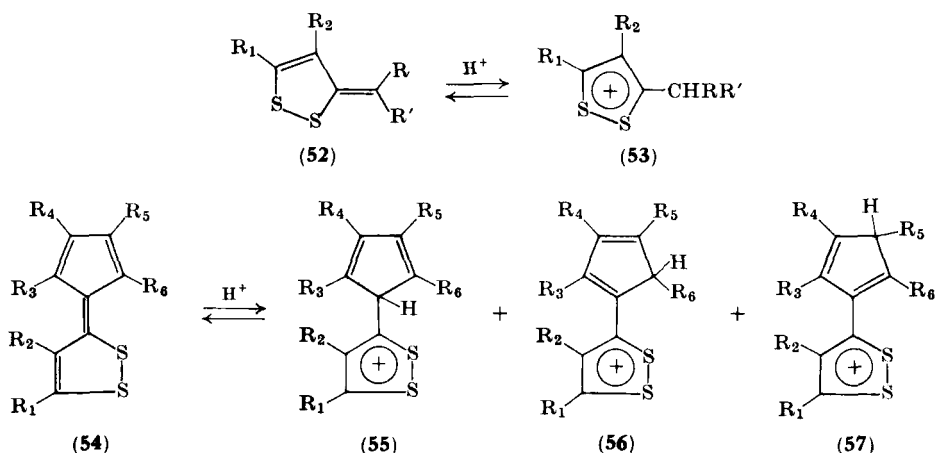
<sup>68</sup> M. Schmidt and T. Sand, *Ber.* **97**, 282 (1964).

<sup>69</sup> Y. Mollier and N. Lozac'h, *Bull. Soc. Chim. France* p. 614 (1961).

<sup>70</sup> U. Schmidt, R. Scheuring, and A. Lüttringhaus, *Ann.* **630**, 116 (1960).

subject to the same uncertainties as those of the "trithione"-metal salt adducts.

The "trithione"-methides (3-methylene-1,2-dithioles) are iso- $\pi$ -electronic with the heptafulvenes,<sup>71</sup> and possess a basicity comparable to that of the latter. Some true 3-alkylated 1,2-dithiolium salts can be obtained by protonation of compounds **52**. This method of preparation is rather narrowly limited, however, by the fact that the simple derivatives of **52** (as in the hydrocarbon series) are evidently very unstable and have not as yet been described. These dithiafulvenes become stable, easily handled compounds only when they contain aryl or typical acceptor residues (R and/or R' = CN, CO<sub>2</sub>R) in the 6-position.<sup>53, 72</sup> This substitution, however, again as in the hydrocarbon series,<sup>73</sup> lowers the basicity to such an extent that the dinitrile (**52**) (R<sub>1</sub> = R<sub>2</sub> = H, R = R' = CN), for example, is not appreciably protonated even in pure trifluoroacetic acid.<sup>52</sup>



Protonation does occur, however, in the case of the 1,2-dithiafulvenes (**54**), which are iso- $\pi$ -electronic with the hydrocarbon sesquifulvalene<sup>74</sup>; the favored product is the cation that is most stable in the particular case in question, i.e., the 3-alkyl- (**55**) or 3-alkenyl- 1,2-dithiolium salts (**56** and/or **57**)<sup>45, 53</sup> (Tables IV and V).

<sup>71</sup> W. von E. Doering and D. W. Wiley, *Tetrahedron* **11**, 183 (1960).

<sup>72</sup> Y. Mollier and N. Lozac'h, *Bull. Soc. Chim. France* p. 157 (1963).

<sup>73</sup> T. Mukai, T. Nozoe, K. Osaka, and N. Shishido, *Bull. Chem. Soc. Japan* **34**, 1384 (1961).

<sup>74</sup> H. Prinzbach and W. Rosswog, *Tetrahedron Letters* **19**, 1216 (1963).



TABLE IV

3-ALKYL-1,2-DITHIOLIUM SALTS (55) BY PROTONATION OF  
1,2-DITHIAFULVALENES<sup>a</sup>

R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub> /R <sub>4</sub>	R <sub>5</sub> /R <sub>6</sub>
C <sub>6</sub> H <sub>5</sub>	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>4</sub> —OH (4)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,4)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,5)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (3,4)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
C <sub>6</sub> H <sub>2</sub> —(OCH <sub>3</sub> ) <sub>3</sub> (2,4,6)	H	C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>
—C <sub>4</sub> H <sub>4</sub> —		C <sub>4</sub> H <sub>4</sub>	C <sub>4</sub> H <sub>4</sub>

<sup>a</sup> Data taken from E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

TABLE V

3-ALKENYL-1,2-DITHIOLIUM SALTS (56) BY PROTONATION  
OF 1,2-DITHIAFULVALENES<sup>a</sup>

R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub> = R <sub>4</sub> = R <sub>5</sub> = R <sub>6</sub>
C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>
C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	C <sub>6</sub> H <sub>5</sub>
C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	C <sub>6</sub> H <sub>5</sub>
C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	C <sub>6</sub> H <sub>5</sub>
—C <sub>4</sub> H <sub>4</sub> —		C <sub>6</sub> H <sub>5</sub>
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>
C <sub>6</sub> H <sub>5</sub>	H	Cl
C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	Cl

<sup>a</sup> Data taken from E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

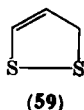
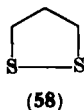
## B. CHEMICAL PROPERTIES

## 1. General Remarks

In comparison with the highly strained (Bergson and Schotte<sup>75</sup> quote a minimum strain of 16 kcal/mole on the basis of crystal struc-

<sup>75</sup> G. Bergson and L. Schotte, *Acta Chem. Scand.* **12**, 367 (1958).

ture analysis) and consequently readily polymerizable 1,2-dithiolane<sup>76, 77</sup> (58), or with 1,2-dithiole (59),<sup>78</sup> which, according to reports



so far, is incapable of existing even in dilute solution, the 1,2-dithiolium ion (1) is surprisingly stable. It is similar in this respect to the thermally very stable "trithiones" or to the structurally related "thiurets,"<sup>79</sup> with which it probably shares the property of having a practically planar structure (Section II, C, 2).

Unfortunately, no quantitative investigations yielding accurate data on the thermodynamic stability of the parent system, or even leading to estimated relative values by comparison with other iso- $\pi$ -electronic ions, have so far been carried out. There is some qualitative evidence indicating that the 1,2-dithiolium salts are generally less susceptible to solvolysis than are the tropylium salts.<sup>79a</sup> These properties are naturally also determined to the usual extent by the nature of the anion; since the anions are very readily interchangeable, both the very water-soluble hydrogen sulfates or monomethyl sulfates and the more lipophilic bromides or perchlorates can be obtained. However, the addition products of the "trithiones" with halogens and acid chlorides, which we have also classified (albeit with certain reservations) as derivatives of the 1,2-dithiolium system (Section II, A, 2, c), are extremely sensitive towards hydrolysis. In agreement

<sup>76</sup> A. Schöberl and H. Gräffe, *Ann.* **614**, 66 (1958).

<sup>77</sup> G. Bergson, Dissertation, Uppsala (1962); U. Schmidt, P. Grafen, and H. W. Goedde, *Angew. Chem.* **77**, 900 (1965).

<sup>78</sup> A. Lüttringhaus, Personal communication.

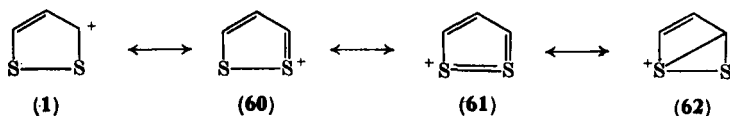
<sup>79</sup> F. Kurzer, *Chem. Rev.* **56**, 95 (1956).

<sup>79a</sup> Such behavior would be in agreement with  $pK_R^+$  determinations by R. Pettit *et al.*<sup>79b</sup> made for several aromatic sulfur-containing cations—though not for 1,2- or 1,3-dithiolium salts—and for their isoelectronic homonuclear carbon cations. Replacement of a double bond by a sulfur atom is found to considerably enhance the stability (as measured by the electrophilicity) of the cation. HMO calculations suggest that the reason for the increased stability of the sulfur-containing cations is that the conjugate bases of these systems possess a much lower  $\pi$ -electron bonding energy than the carbon systems.

<sup>79b</sup> R. G. Turnbo, D. L. Sullivan, and R. Pettit, *J. Am. Chem. Soc.* **86**, 5630 (1964).

with the earlier findings in the tropylium<sup>20</sup> and thiopyrylium<sup>25, 27</sup> series, the fused-ring salts appear to be less stable.

The 1,2-dithiolium salts are electron-deficient compounds, and as such are very reactive and unselective towards nucleophilic reagents. Qualitative considerations based on the simple resonance theory, as well as refined quantum mechanical approximations (Section II, C, 1), indicate that the resonance hybrid is most closely described by the carbonium and sulfonium structures (1 and 60), whereas the "deceit" (61) and "long-bond" (62) structures appear to be of little importance. As would be expected for a charge distribution indicated in 1, protons attached in positions 3 and 5 experience a relatively weak electron screening effect (Section II, C, 4).<sup>79c</sup>



Although nucleophilic attack takes place preferentially in these two positions, very "thiophilic" groups must also be expected to attack one of the sulfur atoms, leading either to cleavage of the disulfide bridge or (less likely) to occupation of a *d* orbital of the sulfur.<sup>80</sup>

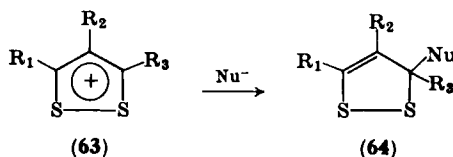
As we shall see in the next section, these expectations are largely fulfilled. It should, however, be pointed out here and now that our present knowledge and ideas regarding the chemical behavior of the 1,2-dithiolium system are largely based on the reactions of more or less highly aryl-substituted derivatives. Relatively few investigations have as yet been carried out on the parent system itself, for a number of reasons. Thus the aryl-substituted derivatives are more readily obtainable and in greater variety than the parent system, as well as being more stable. The deciding factor in the choice of substrate, however, is probably the fact that only those reactions that involve aryl-substituted derivatives have any preparative value, and these

<sup>79c</sup> The prototropic mobility of these hydrogens is far weaker than of H-2 in the 1,3-dithiolium system (Section III, B, 1), as would be expected. The effective half-life of hydrogen deuterium exchange in the case of the 4-phenyl-1,2-dithiolium chloride [10% (v/v) CF<sub>3</sub>CO<sub>2</sub>D/D<sub>2</sub>O; 74°] was determined as 11.6 ± 1 minutes.<sup>79d</sup>

<sup>79d</sup> H. Prinzbach, E. Futterer, and A. Lüttringhaus, *Angew. Chem.* **78**, 492 (1966).

<sup>80</sup> G. Suld and C. C. Price, *J. Am. Chem. Soc.* **83**, 1770 (1961).

are in fact the only reactions that generally yield identifiable products. With only a few highly substituted exceptions, the 1,2-dithiole derivatives obtained as the primary products of additions to **63** in the 3- or 5-positions are very unstable and decompose rapidly; the type of decomposition again depends on the nature of the substituents Nu, R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>. When R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H, **64** decomposes in a

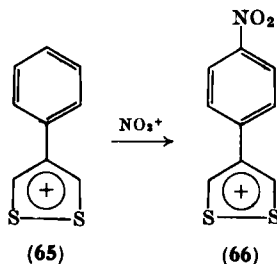


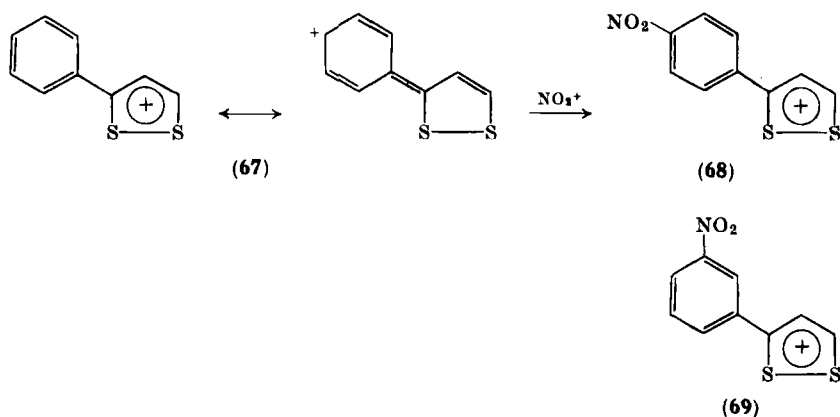
complex sequence of redox reactions. Aryl substituents in the ring, on the other hand, stabilize certain transition states, and so direct the decomposition along certain preferred paths. These substituents naturally also influence the position at which the nucleophilic attack on the ring takes place.

## 2. Reactions with Electrophilic Reagents

Like other cations, such as the tropylium ion, the 1,2-dithiolium ring is stable towards electrophilic reagents. Thus the salts remain unchanged on storage for long periods in concentrated sulfuric acid, for example.<sup>43</sup>

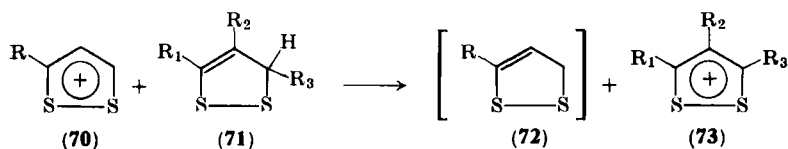
An interesting point in this connection, however, is the fact that not only can the 4-phenyl derivative (**65**) be nitrated to form **66** (the transmission of the electron deficiency into the 4-phenyl substituent is relatively weak), but the 3-phenyl derivative (**67**) can also be nitrated to give **68** and **69**. A possible explanation for this is that the decrease in the electron density in the 4-position of the substituent, as expressed by the canonical structures (**67**), favors electrophilic attack of the NO<sub>2</sub><sup>+</sup> ion in the 3'-position.<sup>43</sup>





### 3. Reactions with Nucleophilic Reagents

In close parallel with the oxidation of tropilidene derivatives by tropylium salts,<sup>81</sup> for example, 1,2-dithiolium salts containing a single substituent in position 4 or 5, e.g. **70**, can capture a hydride anion from the doubly substituted, highly strained leuco bases (**71**), thus oxidizing the latter to the more highly substituted and thermodynamically more stable salts (**73**).<sup>82</sup>



The resulting reduction products, i.e., the 1,2-dithioles (**72**), are unstable, and decompose in secondary reactions which are not at present fully understood.

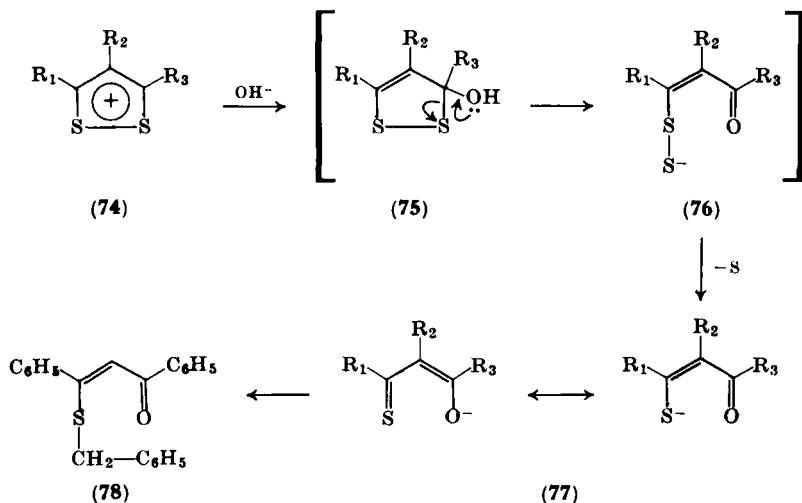
A characteristic property of nearly all 1,2-dithiolium salts is their extremely high sensitivity towards aqueous bases. Monoaryl derivatives decompose almost instantaneously in the presence of hydroxide ions, with liberation of elementary sulfur. Any explanation that may be given is subject to a great deal of uncertainty in view of the speed and complexity of the decomposition. It appears plausible, however,

<sup>81</sup> A. P. Ter Borg, R. van Helden, A. F. Bickel, W. Renold, and A. S. Dreiding, *Helv. Chim. Acta* **43**, 457 (1960).

<sup>82</sup> E. Klingsberg, *J. Am. Chem. Soc.* **85**, 3244 (1963).

that the hydroxide ion first attacks in position 3 or 5, and that the resulting 1,2-dithiole (75) decomposes by ring cleavage to form  $\alpha,\beta$ -unsaturated ketones (76), which are very sensitive to alkali; these ketones should then readily lose elementary sulfur.

In support of this mechanism, the ambident anion (77) formed by the loss of sulfur from 76 has been intercepted by benzyl chloride in the case of the 3,5-diphenyl-1,2-dithiolium salt.<sup>24</sup>



Since the hydroxide ion has been found to be strongly thiophilic towards disulfides,<sup>83</sup> direct attack on the disulfide bridge of 74 must also be expected.

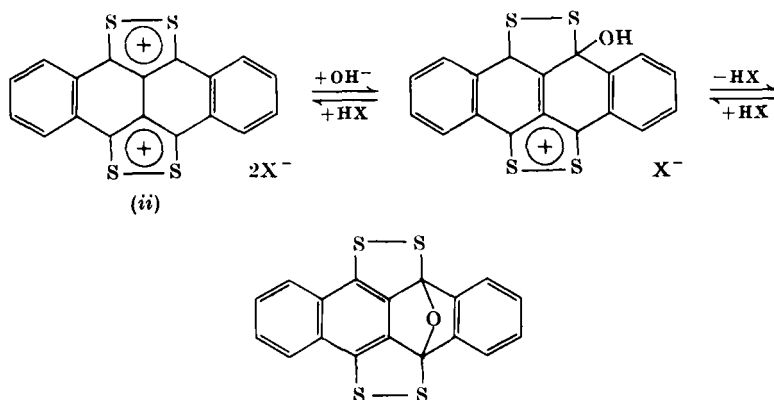
The primary adduct, corresponding to 75, in the case of the dication (ii) (Section II, A, 2, a) does not undergo ring cleavage but is stabilized to a blue-green product to which the structure of the endo oxide is assigned on the basis of the data presently available.

The ion radical (iii) ( $\text{R}^+\text{X}^-$ ) in aqueous KOH solution yields, without elimination of sulfur, a product of the composition  $\text{R}_2\text{O}$ , the structure of which is still unknown.

The action of hydroxide ions on salts containing typical electron-donating groups in positions 3 and 5 leads to a complex redox reaction; dithiomalonamide and cyanothioacetamide have been detected as

<sup>83</sup> W. A. Pryor, "Mechanism of Sulfur Reactions," p. 60. McGraw-Hill, New York, 1962.

cleavage products in the reaction of an aqueous solution of the diamine (15) with sodium hydroxide.<sup>9</sup>



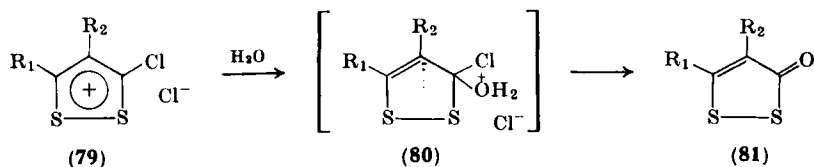
Our knowledge of the breakdown mechanism of "trithionium salts" in alkaline media is not much better. Böttcher in his classic investigations found small quantities of the "Baumann-Fromm disulfide" as a product of the reaction of potassium hydroxide with the "anethole-trithionium salt"; subsequent detailed studies, however, failed to yield any further information. The reaction leads to a large number of products, even when a relatively mild base such as sodium acetate in aqueous pyridine is used.<sup>84</sup> The same is true of the reactions of "trithionium salts" with sodium alkoxides. Alkoxide-catalyzed reactions of these salts are therefore rarely of any preparative value. The above mechanism for the action of alkalies on dithiolium salts, in which cleavage is assumed to occur at the hemithioacetal stage (75), is confirmed by a number of more recent discoveries. Thus 3-chlorinated dithiolium salts (79) are hydrolyzed in acidic media, giving very high yields of "Baumann-Fromm disulfides" (81)<sup>10, 11, 12, 13, 44, 50, 85</sup>; the intermediate 80 is stabilized by elimination of HCl instead of by ring opening. The analogous reaction in the chemistry of the iso- $\pi$ -electronic hydrocarbons is the ready hydrolysis of the bromotropylum salts.<sup>86</sup>

<sup>84</sup> R. Scheuring-Deckert, Dissertation, Freiburg-im-Breisgau (1957).

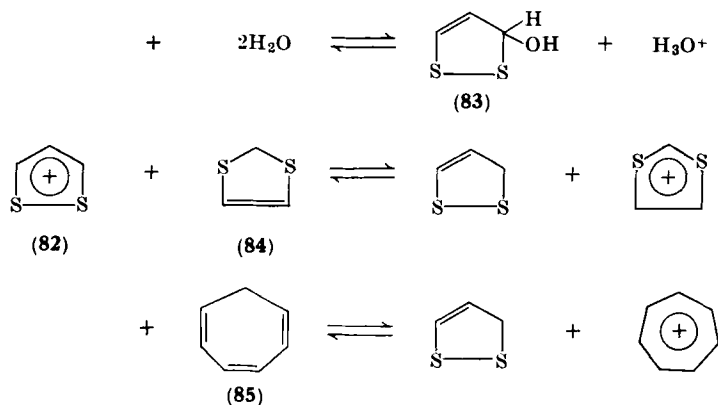
<sup>85</sup> F. Boberg and A. Marei, *Ann.* **666**, 88 (1963); F. Boberg, *Ann.* **681**, 169, 178 (1965).

<sup>86</sup> D. N. Kursanov, *Uch. Zap. Khar'kovsk Gos. Univ. Tr. Khim. Fak. i Nauchn.-Issled. Inst. Khim.* **17**, 7 (1961); see *Chem. Abstr.* **58**, 4398 (1963).

The instability of **83** has so far also prevented the accurate measurement of the equilibrium between **82** and **83**, i.e., of the  $pK$  of the "acid"



(82). Some indications in the form of thermodynamic data are expected from a series of hydride-exchange reactions, e.g., with 1,3-dithiole (**84**) or tropilidene (**85**). In view of the large volume of numerical



data on the iso- $\pi$ -electronic cations  $\text{C}_7\text{H}_7^+$ ,  $\text{C}_5\text{H}_5\text{O}^+$ , and  $\text{C}_5\text{H}_5\text{S}^+$ , and on the aryl-substituted, vinylogous aryl-substituted, and fused-ring derivatives of these, collected over the past years by Jutz and Voithenleitner<sup>87</sup> and by Degani *et al.*,<sup>88</sup> it would be of great interest to compare the relative stabilities of these cations.

The 4-phenyl-1,2-dithiolium salt (**86a**) is decomposed by ethoxide ion<sup>24</sup>; the only product that can be isolated is the sulfurization product "4-phenyltrithione."<sup>89</sup> In the case of the 3,5-disubstituted

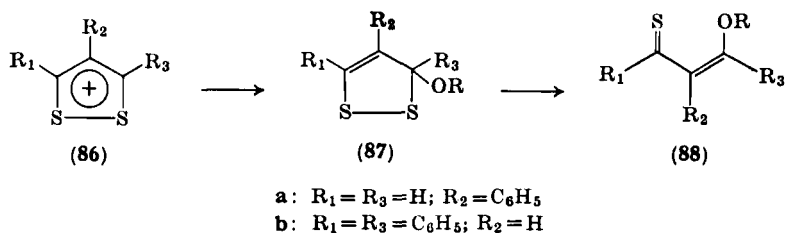
<sup>87</sup> C. Jutz and F. Voithenleitner, *Ber.* **97**, 1590 (1964), and earlier work in this field.

<sup>88</sup> J. Degani, *Abstr. Papers, Symp. Chem. of Sulfur Compounds*, Prague, Czech. Chem. Soc. p. 26 (1964); J. Degani, R. Fochi, and C. Vincenzi, *Gazz. Chim. Ital.* **94**, 203 (1964).

<sup>89</sup> E. Klingsberg, *J. Org. Chem.* **28**, 529 (1963).

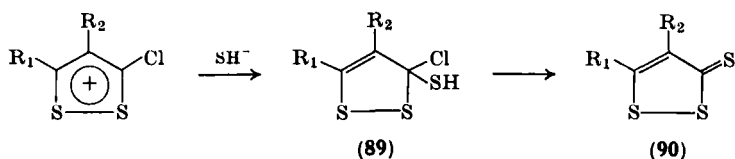


salt (**86b**), on the other hand, it is possible to isolate the colorless ethoxydithiole (**87b**), which is reconverted into the original salt by the action of perchloric acid. The low stability of the addition products (**87**) is even more obvious from the fact that **87b** decomposes during chromatography on a basic alumina column, to give sulfur and another product which is probably the thione (**88b**).<sup>24</sup>

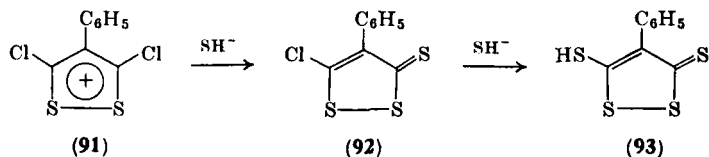


The action of  $SH^-$  or  $SR^-$  on 1,2-dithiolium salts is similar to that of  $OH^-$  or  $OR^-$ . Thus the 3,5-diamino-“1,2-dithiolium” salt (**15**) is very rapidly decomposed by  $SH^-$ , the only reaction product identified again being dithiomalonamide.<sup>9</sup>

The reactions of 3-halogenated dithiolium salts with  $H_2S$  are again of preparative value; the mercapto-1,2-dithiole derivatives (**89**) cannot be isolated, but lose  $HCl$  to form the “trithiones” (**90**).<sup>11</sup>



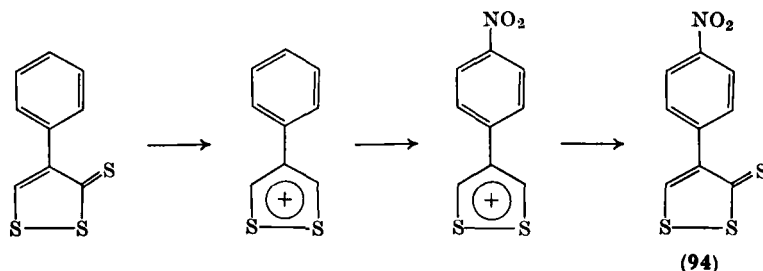
If these salts are also halogenated in position 5, as for example in **91**, the second halogen can be readily substituted at the “trithione” stage (**92**) by  $SH^-$ , with formation of **93**.<sup>90</sup> Mercaptotrithiones obtained in this way are of interest for their fungicidal properties.<sup>90</sup>



<sup>90</sup> L. E. Carosino, U.S. Patent 3,109,772 (Cl. 167-33) (1963); see *Chem. Abstr.* **60**, 2933 (1964).

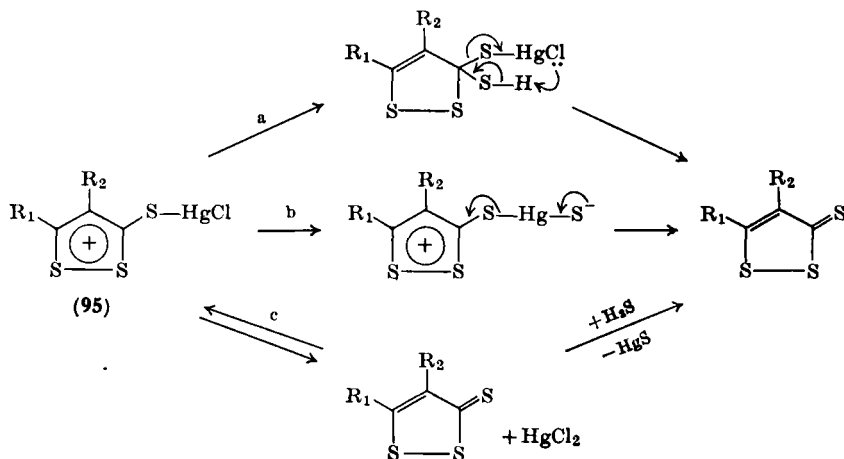
This nucleophilic substitution in the "trithione" ring calls to mind Boberg's report<sup>10, 85</sup> that halogen substituents in the 5-position of "Baumann-Fromm disulfides" are also susceptible to displacement by nucleophilic reagents such as amines.

Another reaction that can be formally grouped with those discussed above is the sulfurization of dithiolium salts with sulfur in pyridine,<sup>79d, 89</sup> in which the sulfur also acts as the oxidizing agent. This reaction enjoys a certain importance as a "trithione" synthesis. Nitro-substituted "trithiones" such as **94** cannot be obtained by the usual methods, since the nitro groups are reduced under the drastic reaction conditions required. These nitro derivatives can, however, be readily obtained by the method outlined in Scheme 4.



SCHEME 4

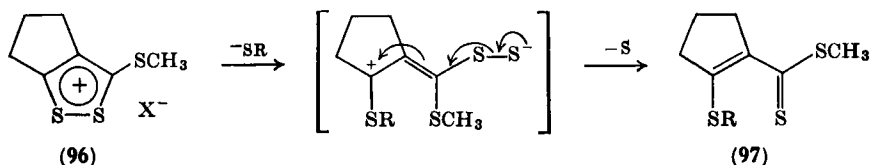
The most important of the reactions of the 1,2-dithiolium system with  $\text{SH}^-$  is the action of  $\text{H}_2\text{S}$  on the "trithione"-metal complexes (**95**) (Section II, A, 2, c), which we have conditionally classified as



dithiolium salts. This reaction in its various modifications is important in the isolation and purification of the "trithiones."

From the point of view of the reaction mechanism, there appear to be arguments in favor of both substitution on C-3 (path a) and substitution on the metal atom (path b). Since, however, a dissociation equilibrium (albeit greatly favoring the adduct) has been detected for complexes of this type in solution,<sup>47a, 55</sup> there is probably something to be said for mechanism c.

Rather surprisingly, in the only reaction so far reported between a "trithionium salt" and a mercaptan, the addition takes place in position 5.<sup>59</sup>



Compound **96** reacts with  $\text{SR}^-$ , with ring cleavage and loss of sulfur, to form the methyl ester of the 1-alkylmercaptocyclopent-1-ene 2-dithiocarboxylic acid (**97**). Compound **96** reacts in a similar manner with primary amines (see below).

Few regular features have been found in the reactions with ammonia; the course of the reaction again largely depends on the number and nature of the substituents attached to the hetero ring. The situation is illustrated by the following examples. If the 3,5-diphenyl salt (**98**) is treated in alcoholic solution with  $\text{NH}_3$ , the reaction proceeds in accordance with Scheme 5; i.e., an S atom is replaced by N, as in the reaction of pyrylium<sup>91, 92</sup> and thiopyrylium<sup>93</sup> salts with  $\text{NH}_3$ .

3,5-Diphenylisothiazole (**99**) can be obtained by this method in a yield of about 50%.<sup>24</sup> The same result has also been found for the 4-phenyl-1,2-dithiolium salt (88% yield of 4-phenylisothiazole).<sup>94</sup> The course of this reaction evidently depends mainly on the solvent. In benzene, for example, only small yields of 4-phenylisothiazole are obtained, the principal product isolated being the bisdithiolyl

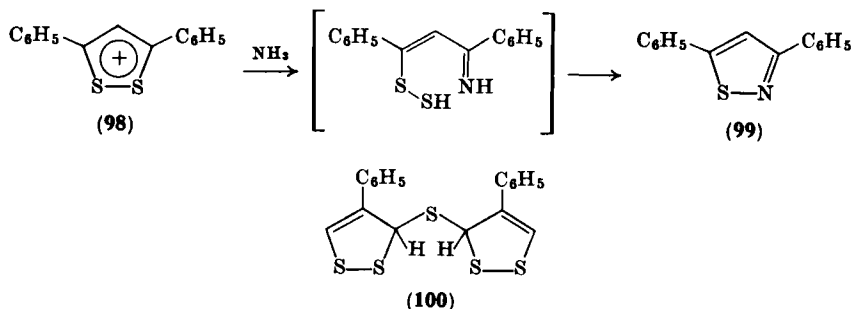
<sup>91</sup> K. Dimroth, *Angew. Chem.* **72**, 331 (1960).

<sup>92</sup> E. Shaw, "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Part 2, Chapter III. Wiley (Interscience), New York, 1961.

<sup>93</sup> R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 207 (1956).

<sup>94</sup> R. A. Olofson, J. M. Landesberg, and R. O. Berry, *Abstr. Papers 144th Meeting, Los Angeles, Am. Chem. Soc.* p. 45M (1963).

sulfide (100). The formation of the latter is explained by the reaction of two dithiolium cations with one molecule of  $\text{H}_2\text{S}$ , part of which is derived from the ring-closure step in the formation of the isothiazole.



SCHEME 5

The tropylium cation reacts with  $\text{H}_2\text{S}$  in the same way, to form dithiopyl sulfide.<sup>95</sup>

Rather surprisingly, the product of the reaction between the 3,4-diphenyl-1,2-dithiolium salt and ammonia in ethanol was found to contain 4,5-diphenyltrithione, but no isothiazole, although the reaction with phenylhydrazine gave a 95% yield of the corresponding pyrazole.<sup>45</sup>

Judging from these early results, it appears that the reaction of 1,2-dithiolium salts with ammonia offers an elegant synthesis of certain substituted isothiazoles that are difficult to obtain by other methods.<sup>96</sup> The reaction of the unsubstituted 1,2-dithiolium salt with  $\text{NH}_3$ , however, does not yield the parent isothiazole system. Moreover, in the case of the 3(5)-methyl salts, the abstraction of a methyl proton activated by the positive charge of the ring successfully competes with this reaction (Section II, B, 4).<sup>14a</sup>

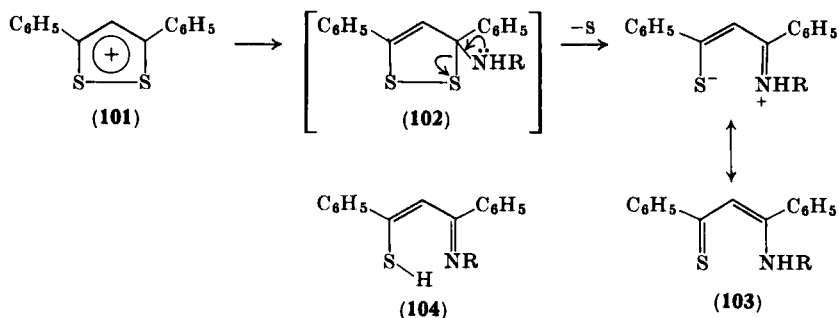
There are at present no detailed data available as to whether and to what extent the formation of isothiazoles from unsymmetrically monoaryl-substituted 1,2-dithiolium salts is stereoselective, or how the ratio of the isomers can be influenced by variation of the substitution.

The behavior of the 3- and 5-phenyl salts such as **101** towards

<sup>95</sup> W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **79**, 352 (1957).

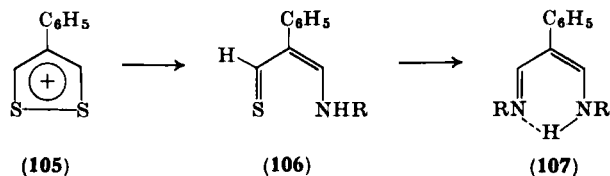
<sup>96</sup> F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and H. Hoffmann, *Angew. Chem.* **75**, 1189 (1963).

primary and secondary amines such as aniline, *N*-methylaniline, or piperidine is basically similar to their behavior towards  $\text{NH}_3$  (Scheme 6). The initial product (102) undergoes ring cleavage with simultaneous elimination of elementary sulfur. On the basis of spectroscopic data, the products of the reaction with primary amines have been assigned the thione structure (103), and not the tautomeric mercapto-anil structure (104).<sup>24</sup>



SCHEME 6

Some of these aminothiones react further with excess amine; thus the *cis* isomer of the malonic dialdehyde dianil (107) has been obtained by the reaction of the 4-phenyl-1,2-dithiolium salt (105) with two moles of aniline.<sup>24</sup>



In the reaction of "trithionium salts" (108) with primary and secondary amines in general the ring skeleton remains intact<sup>58, 59, 97, 98a, b, c</sup>;

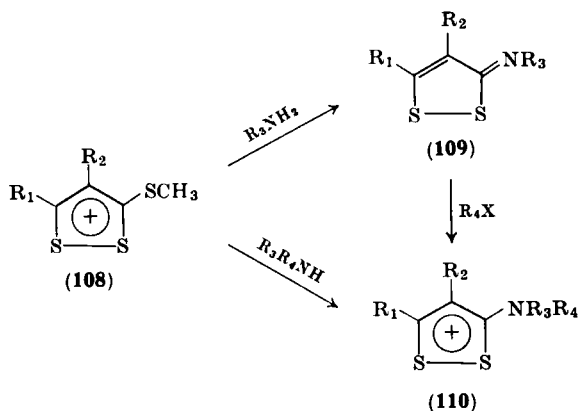
<sup>97</sup> B. Böttcher, German Patent 941, 669 (Cl. 12q, 27) (1956); see *Chem. Abstr.* **53**, 409 (1959).

<sup>98a</sup> U. Schmidt, A. Lüttringhaus, and F. Hübinger, *Ann.* **631**, 138 (1960).

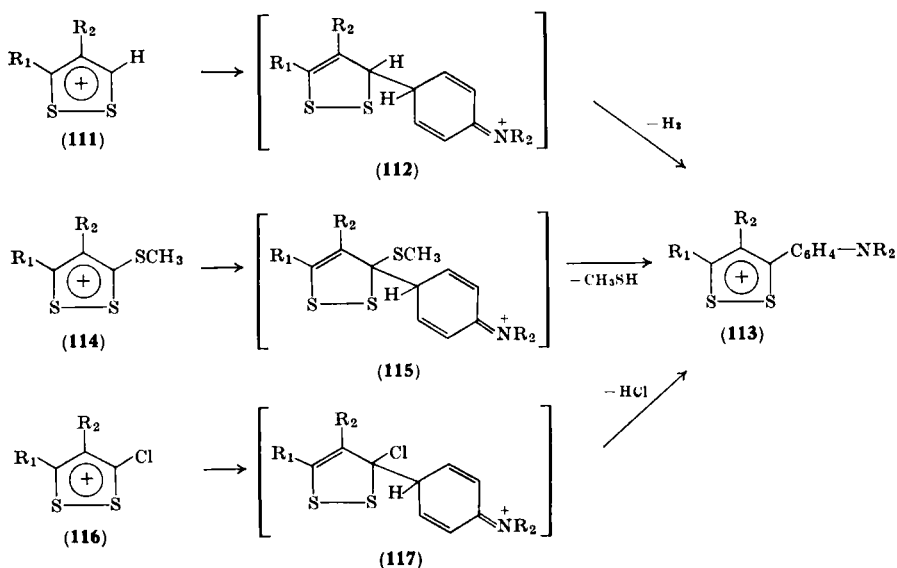
<sup>98b</sup> R. Pinel, Y. Mollier, and N. Lozac'h, *Compt. Rend.* **260**, 5065 (1965).

<sup>98c</sup> C. Paulmier, Y. Mollier, and N. Lozac'h, *Bull. Soc. Chim. France*, 2463 (1965).

these reactions always lead to high yields of the Schiff's bases (**109**) and the amino-substituted 1,2-dithiolium salts (**110**). The salts (**110**) can also be obtained by alkylation of the Schiff's bases.

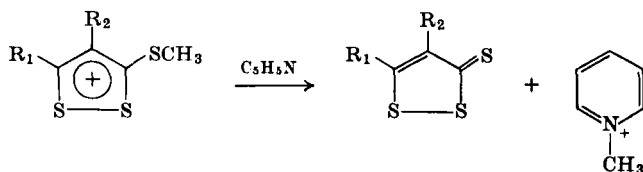


1,2-Dithiolium salts (**111**) with no substituent in position 3 readily undergo a single-step reaction with dimethylaniline to form the new 1,2-dithiolium salts (**113**). The thermodynamically less stable salt (**111**) again acts as an oxidizing agent, as discussed earlier.<sup>23</sup>



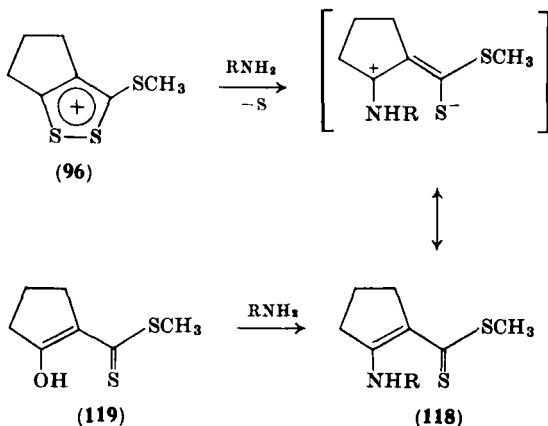
Dimethylaniline is also *C*-alkylated by trithionium salts (**114**)<sup>70</sup> or chloro-1,2-dithiolium salts (**116**),<sup>11</sup> with elimination of methyl mercaptan or hydrogen chloride to form **113**.

It is not known yet whether the 1,2-dithiolium salts are sufficiently electrophilic to attack even benzene derivatives containing less efficient electron-donating groups. In any case "trithionium salts," with their already weaker electrophilic character, are unable to substitute phenols<sup>70</sup>; recently, substitution of phenolate has been reported.<sup>98b</sup>



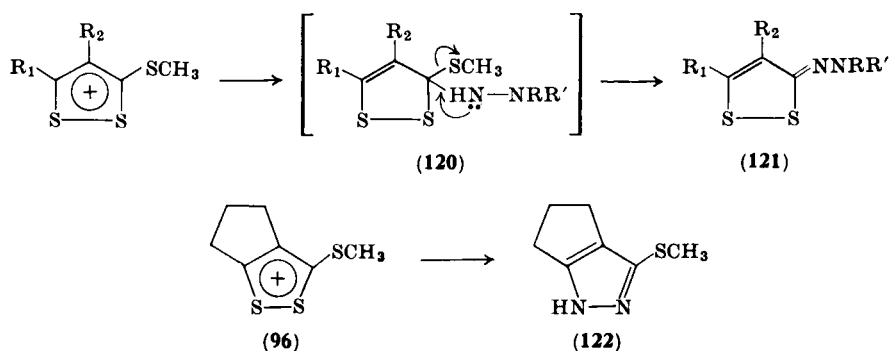
Tertiary amines such as pyridine or acridine are methylated by "methyl trithionium salts."<sup>58, 60</sup>

No reactions of either 1,2-dithiolium salts or "trithionium salts" with hydroxylamine have been described in the literature. The explanation in the case of the "trithionium salts" is probably the fact that the expected condensation products, i.e., the oximes of the "Baumann-Fromm disulfides," can be obtained via the trithiones themselves<sup>2</sup>; this is one of the few examples in which trithiones react with carbonyl reagents without undergoing cleavage of the 1,2-dithiole ring.



The addition of amine to the bicyclic salt (**96**) initially takes place not in position 3, but in position 5, as in the reaction with mercaptans; the reaction then proceeds by the same steps to yield the ester of the 1-aminocyclopent-1-ene 2-dithiocarboxylic acid (**118**). This ester (**118**) is obtained in yields of 30–65%; its structure has been confirmed by independent synthesis from **119**. This reaction course is again confined to the special system **118**, the homologous “tetramethylene-trithionium salts” yielding Schiff’s bases on reaction with primary amines under the same conditions.<sup>59</sup>

Intensive studies have been devoted to the behavior of the 1,2-dithiolium<sup>43</sup> and “trithionium” salts<sup>58, 98 a, b, c</sup> towards hydrazine and substituted hydrazines. With only one exception, which will be mentioned below, all these reactions lead to addition of the base in position 3 or 5 to form the intermediates **120** or **124**, which cannot be isolated. The intermediates **120** rapidly eliminate the good leaving



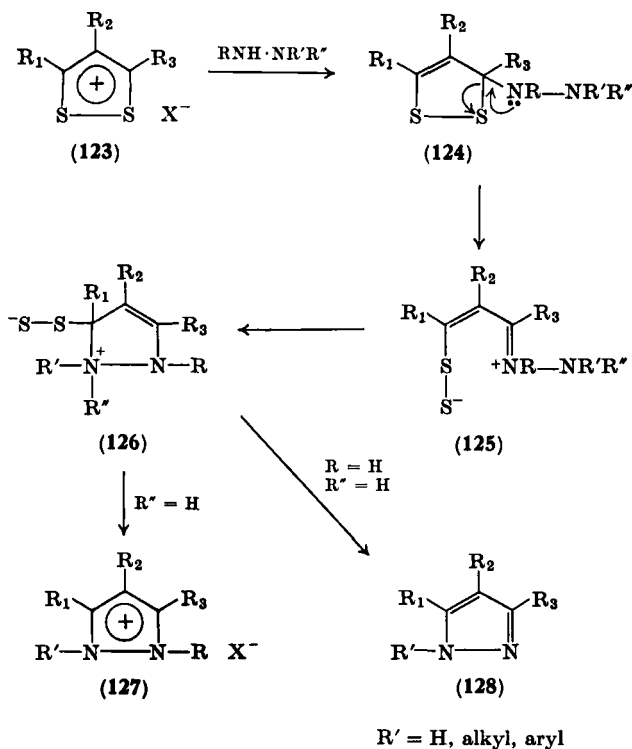
group CH<sub>3</sub>S<sup>-</sup> to form azines, phenylhydrazones, and many other condensation products (some of which are of pharmacological interest) which cannot be prepared by the reaction of “Baumann–Fromm disulfides” or “trithiones” with the corresponding carbonyl reagents.

The behavior of **96** towards hydrazines, as towards mercaptans (leading to **97**) and primary amines (leading to **118**), is “abnormal” in that the nucleophilic attack by the base takes place in position 5. The reaction (both the product and the probable mechanism of which are reminiscent of the action of hydrazines on 1,2-dithiolium salts) leads to the methylmercaptopyrazole (**122**).<sup>59</sup>

The free electron pair on the nitrogen in the initial product (**124**) causes displacement of the disulfide group from C-3, with opening of



the ring. As is formally shown in Scheme 7, the ultimate products are pyrazolium salts (**127**) or pyrazoles (**128**), depending on the degree of substitution of the hydrazine used.



SCHEME 7

This pyrazole synthesis, which undoubtedly profits from the thermodynamic stability of the end products, gives excellent yields (Table VI). Its range of application is limited, however, by the fact that the reaction of 3-substituted unsymmetrical dithiolium salts with substituted hydrazones leads to mixtures of isomers which can be separated only with difficulty. On the other hand, it does permit the preparation of a single 4,5-disubstituted pyrazole from a 3,4-disubstituted salt and a substituted hydrazine.

As can be seen from Table VII, quaternary pyrazolium salts have so far been obtained only from 4-substituted ( $\text{R}_2$ ) dithiolium salts.

TABLE VI  
 PYRAZOLES (128) FROM 1,2-DITHIOLIUM SALTS

R'	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)	Reference
H	H	C <sub>6</sub> H <sub>5</sub>	H	100	<i>a</i>
H	H	H	C <sub>6</sub> H <sub>5</sub>	—	<i>a</i>
CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	—	<i>a</i>
C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	—	<i>a</i>
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	95	<i>b</i>
2-Benzothiazolyl	H	C <sub>6</sub> H <sub>5</sub>	H	100	<i>a</i>
C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	C <sub>6</sub> H <sub>5</sub>	H	> 80	<i>a</i>
C <sub>6</sub> H <sub>4</sub> —CO <sub>2</sub> H (4)	H	C <sub>6</sub> H <sub>5</sub>	H	> 80	<i>a</i>
C <sub>6</sub> H <sub>3</sub> —Cl <sub>2</sub> (2,5)	H	C <sub>6</sub> H <sub>5</sub>	H	> 80	<i>a</i>

<sup>a</sup> E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961).<sup>b</sup> E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

The products of these reactions also contain considerable quantities of the corresponding "trithione," the sulfur required for the formation of the latter being supplied by the dithiolium salts in a curious disproportionation reaction. This competing reaction becomes predominant at temperatures above  $-20^{\circ}$ . In the case of the 3-phenyldithiolium salt, the "trithione" is the only isolable product even at low temperatures.

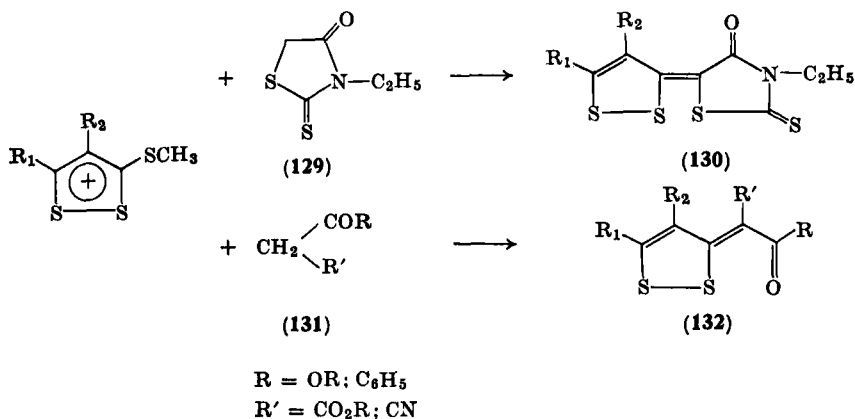
 TABLE VII  
 PYRAZOLIUM SALTS (127) FROM 1,2-DITHIOLIUM SALTS<sup>a</sup>

R = R'	R <sub>1</sub> = R <sub>3</sub>	R <sub>2</sub>	X	Yield (%)
CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub>	62
CH <sub>3</sub>	H	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	ClO <sub>4</sub>	52
C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub>	60

<sup>a</sup> E. Klingsberg, *J. Org. Chem.* **28**, 529 (1963).

*N,N'*-diaryl pyrazolium salts were until recently unknown, and are now obtainable only by this reaction of dithiolium salts, which resembles the formation of pyridinium salts from thiopyrylium salts.<sup>92</sup> Mention should be made of an earlier report, according to which "trithiones" can be condensed with C<sub>6</sub>H<sub>5</sub>NH—NH<sub>2</sub> to form pyrazoloneimide derivatives, although only in modest yields.<sup>57</sup>

The electrophilic behavior of the "trithionium" salts towards C—H acids is again considerably weaker than that of the 1,2-dithiolium salts. Consequently, the reactions of the "trithionium" salts with these acids require catalysis by more or less strong bases, according to the acidity of the methylene component. Many doubly activated methylene compounds with cyclic [e.g., rhodanines<sup>58, 72</sup> (such as **129**), pyrazolones,<sup>72</sup> barbituric acid derivatives,<sup>58, 72</sup> dimedeone,<sup>72</sup> indan-1,3-dione,<sup>72</sup> phenalan-1,3-dione<sup>72</sup>] and open-chain structures (**131**) [e.g., malonates and their derivatives,<sup>58, 70, 72</sup> benzoylacetonitrile<sup>82, 99</sup>] have been condensed with "trithionium" salts, using pyridine in solvents with low dielectric constants or using pyridinium acetate. The configuration of the condensation products, particularly those obtained from cyclic methylene components, does not appear to have been adequately established in most cases.

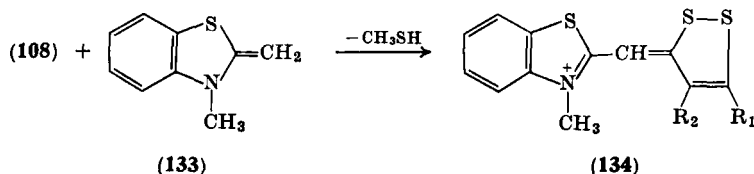


SCHEME 8

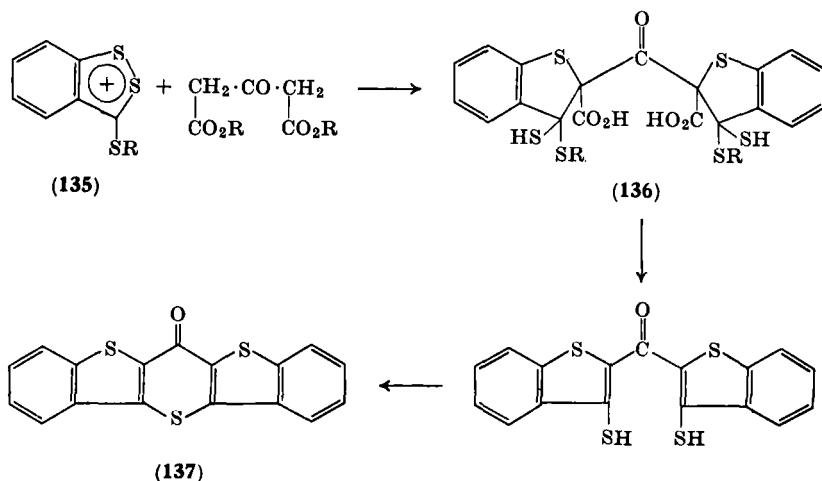
The yields of these reactions again depend largely on the substituents in the dithiolium salt; good yields are obtained from 5-monosubstituted salts, whereas the yields obtained from 4,5-disubstituted salts are only moderate. The "methides" such as 1-methyl-2-methylene-benzothiazoline (**133**) are also sufficiently nucleophilic to react with "trithionium" salts, the product obtained from **108** and **133** being the monomethine **134**.

<sup>99</sup> H. Behringer, M. Ruff, and R. Wiedenmann, *Ber.* **97**, 1732 (1964); see also R. J. S. Beer, K. C. Brown, R. P. Carr, and R. A. Slater, *Tetrahedron Letters* **24**, 1961 (1965).

A similar mechanism, i.e., electrophilic attack of the cation on the conjugate base, probably also accounts for the formation of cyanine dyes by the autocondensation of 3,4-trimethylene-1,2-dithiolium



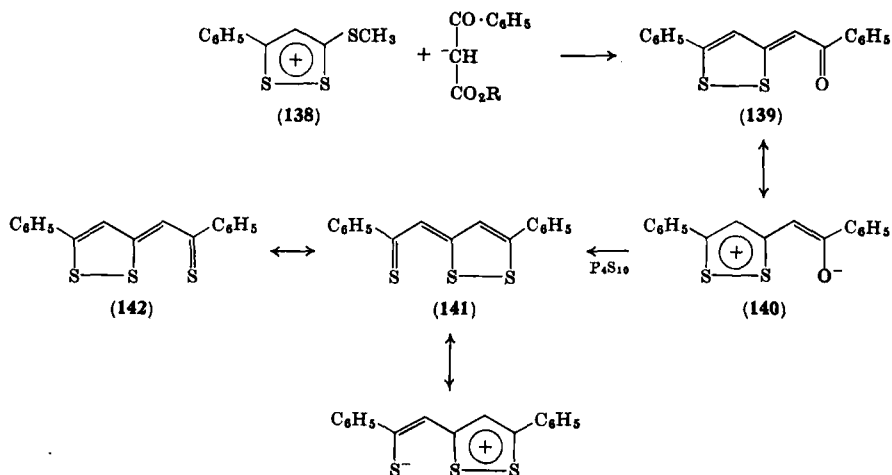
salts; this reaction takes place on heating, even in glacial acetic acid.<sup>59</sup> In addition to reactions of the type shown in Scheme 8, the "benzotrithionium salts" (135) also undergo another type of reaction, which is apparently initiated by attack of the carbanion on the disulfide bridge to form 136, for example. However, the conclusions drawn from the formation of such "anomalous" reaction products as 137, for example, regarding the electron distribution, and hence regarding the bonding in the undisturbed ground state ("ring-chain mesomerism") of the "benzotrithionium salts," are certainly not justified.<sup>100</sup>



$\alpha$ -Methyl ketones, which react with 1,2-dithiolium salts even in boiling ethanol, react with "trithionium salts" only after conversion to their sodium salts. This reaction is not generally useful, since the

<sup>100</sup> U. Schmidt, *Ann.* **653**, 109 (1960).

ring system is very often completely destroyed by strong bases; the salt **138**, however, reacts with the sodium salt of benzoylacetate to give a 46% yield of 3-phenacylidene-5-phenyl-1,2-dithiole (**139**).<sup>101</sup>



Compound **139** and the other derivatives of 3,5-epidithio-2,4-pentadien-1-one (**132**), which are obtained in good yields in accordance with Scheme 8, exhibit only weak ketonic properties. This has been interpreted as resulting from polarization towards the betaine structure (**140**). Similar effects and explanations are already familiar from the cases of tropone<sup>102</sup> and 1,4-thiopyrone.<sup>103</sup>

The reaction of these 1,2-dithiolium betaines (**140**) with  $\text{P}_4\text{S}_{10}$  makes available many derivatives of the meribicyclo-3,5-epidithio-2,4-pentadiene-1-thione ("thiothiophene") system which were obtainable only in small yields by earlier syntheses.<sup>104, 105</sup> This system is extremely interesting from the point of view of bond theory.<sup>106, 107</sup> The symmetry indicated by earlier NMR measure-

<sup>101</sup> D. Leaver and D. M. McKinnon, *Chem. Ind. (London)* p. 461 (1964).

<sup>102</sup> T. Nozoe, in "Non-Benzenoid Aromatic Compounds" (D. Ginsburg, ed.), Chapter VII. Wiley (Interscience), New York, 1959.

<sup>103</sup> L. J. Bellamy, in "Organic Sulfur Compounds" (N. Kharash, ed.), Vol. 1, Chapter 6. Pergamon Press, Oxford, 1961.

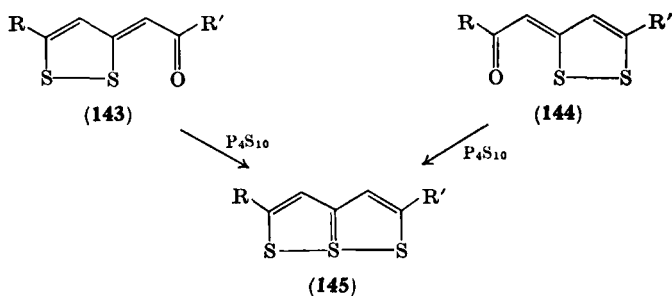
<sup>104</sup> P. Arndt, P. Nachtwey, and J. Busch, *Ber.* **58**, 1633 (1925).

<sup>105</sup> G. Traverso, *Ann. Chim. (Rome)* **44**, 1018 (1954).

<sup>106</sup> J. Giacometti and G. Rigatti, *J. Chem. Phys.* **30**, 1633 (1959).

<sup>107</sup> K. Maeda, *Bull. Chem. Soc. Japan* **34**, 785 and 1166 (1961).

ments<sup>108, 109</sup> and X-ray analysis<sup>110</sup> has been confirmed by chemical methods by French workers,<sup>111</sup> as well as by Klingsberg<sup>82</sup> and Behringer *et al.*<sup>99</sup>; the isomeric *O*-isologs (**143** and **144**) give one and the same product (**145**) on reaction with  $P_4S_{10}$ . The suggestion that this symmetry of the "thiothiophthenes" must be due to a "no-bond resonance" structure as shown in **141** and **142** has been criticized. In the case of the diphenyl derivative, UV spectroscopic data are adduced in support of a rapidly established equilibrium between **141** and **142**.<sup>101</sup>



The "trithionium salts" also condense with the weak C—H acids cyclopentadiene, indene, and fluorene, but again only when the latter are present as their sodium salts. As we have already pointed out, however, the reactions with such strong bases are rather unpredictable, and the desired 1,2-dithiafulvalenes (**146**) may be obtained (if at all) only in very low yields, together with a large number of by-products. The formation of some of these by-products is attributed to the fact that the 1,2-dithiafulvalenes, like the sesquifulvalenes, also react as fulvenes and add on strong bases.<sup>112</sup>

The reaction of **108** with the sodium salt of tetraphenylcyclopentadiene, on the other hand, yields only two products, namely **146a** and another compound which has been provisionally assumed to possess the spiro structure (**149a**). The formation of **149a** can be explained by the attack of a carbanion on the disulfide bridge of **108**, followed by the formation of the sodium salt of **148a**, and finally a

<sup>108</sup> A. A. Bothner-By and G. Traverso, *Ber.* **90**, 453 (1957).

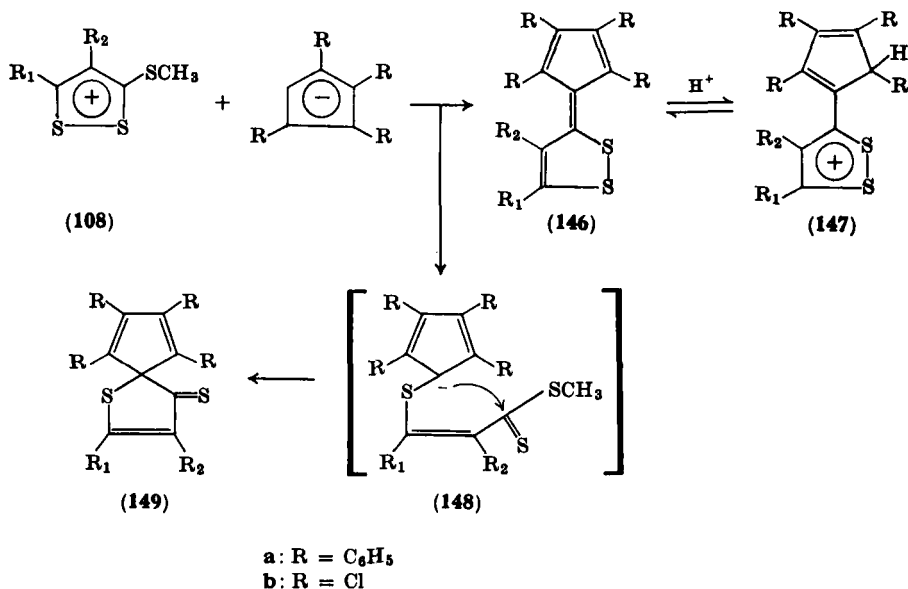
<sup>109</sup> H. G. Hertz, G. Traverso, and W. Walter, *Ann.* **625**, 43 (1959).

<sup>110</sup> S. Bezzi, M. Mammi, and C. Garbuglio, *Nature* **182**, 247 (1958); M. Mammi, R. Bardi, G. Traverso, and S. Bezzi, *ibid.* **192**, 1282 (1961).

<sup>111</sup> G. Pfister-Guillouzo and N. Lozac'h, *Bull. Soc. Chim. France* p. 153 (1963).

<sup>112</sup> K. Hafner, *Angew. Chem.* **75**, 1041 (1963).

second attack on the dithioester group with elimination of the mercaptide ion.<sup>53</sup>

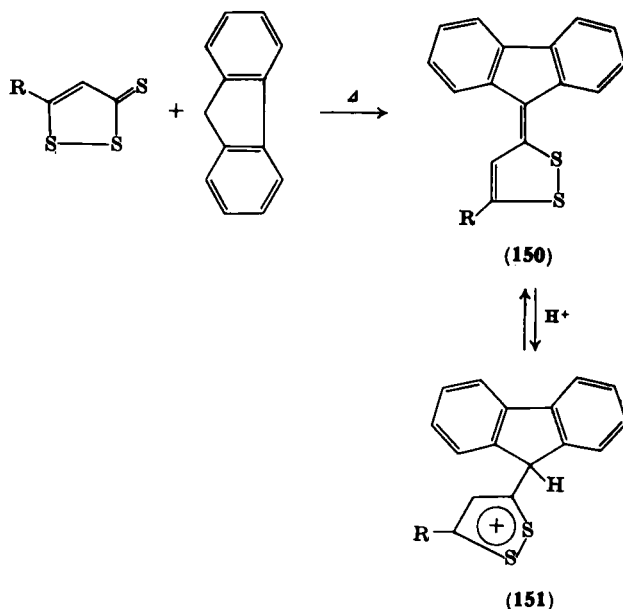


Another competing reaction that generally hinders the condensation with C—H acids is the attack of the carbanion on the *S*-methyl group with displacement of the "trithione." This *C*-methylating power of the "trithionium salts" has been observed, e.g., in the reaction of sodium acetoacetate or the sodium salt of fluorene on 108.<sup>52,58</sup>

The condensation of "5-aryltrithionium salts" (but not of the 4-substituted analogs) with tetrachlorocyclopentadiene proceeds without interference from side reactions. The reaction takes place in methanol at 20° without added base, and gives high yields of the only product, namely tetrachlorodithiafulvalene (146b).<sup>45</sup>

The 1,2-dithiafulvalenes of the type 150, which are obtained (if at all) only in extremely small yields by the reaction of the sodium salt of fluorene with 108 or 111, can be prepared in useful yields from fluorene and "trithione" by a pyrolytic reaction. "Trithiones" with substituents in position 4, however, do not condense with fluorene under these conditions, probably because of steric factors. Attempts to condense indene with "5-aryltrithiones" have also met with failure.<sup>45</sup>

Like the iso- $\pi$ -electronic sesquifulvalenes and their iso- $\pi$ -electronic *O*-<sup>113, 114</sup> and *N*-analogs,<sup>51, 115-118</sup> these 1,2-dithiafulvalenes (**146** and **150**) are strong bases, and are fully protonated even by moderately



strong acids. The site of the electrophilic attack, and hence the structure of the conjugate acids **147** and **151**, has been determined from UV (Section II, C, 3) and NMR (Section II, C, 4) studies.

#### 4. Side Chain Reactivity

The electron deficiency in the 1,2-dithiolium ring is manifested in the acidity of CH, OH, SH, and NH groups attached in positions 3 or 5. The anhydro bases of the corresponding 1,2-dithiolium salts, which are formed even in the presence of very weak bases, may either

<sup>113</sup> A. Schönberg and M. M. Sidky, *J. Am. Chem. Soc.* **81**, 2259 (1959).

<sup>114</sup> G. V. Boyd, *Proc. Chem. Soc.* p. 93 (1959).

<sup>115</sup> F. Kröhnke, K. Ellegast, and E. Bertram, *Ann.* **600**, 176 (1956).

<sup>116</sup> D. N. Kursanov, N. K. Baranetskaya, and V. N. Setkina, *Dokl. Akad. Nauk SSSR* **113**, 116 (1957); see *Chem. Abstr.* **51**, 14711 (1957).

<sup>117</sup> J. A. Berson, E. M. Evleth, and Z. Hamlet, *J. Am. Chem. Soc.* **82**, 3793 (1960); **87**, 2887 (1965).

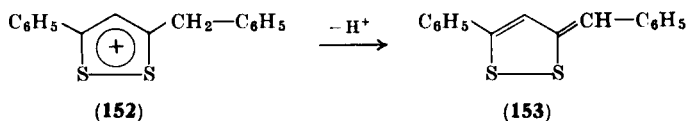
<sup>118</sup> G. V. Boyd and L. M. Jackman, *J. Chem. Soc.* p. 548 (1963).



be isolated as such or enter into fast secondary reactions, depending on the reaction conditions.

The 3-alkyl-1,2-dithiolium salts (**151**) and 3-alkenyl-1,2-dithiolium salts (**147**) obtained from the reaction of 1,2-dithiafulvalenes with trifluoroacetic acid or tetrafluoroboric acid, for example, can be reconverted smoothly and without side reactions into the original bases by addition of bases such as ammonia or even water (Section II, A, 2, c).<sup>45, 52</sup>

The benzyl derivative (**152**) is deprotonated to the crystalline 1,2-dithiafulvene (**153**) by aqueous soda solution. The ease of formation and the stability of these 3-methylene derivatives are strongly influenced by the substituents.<sup>119</sup>



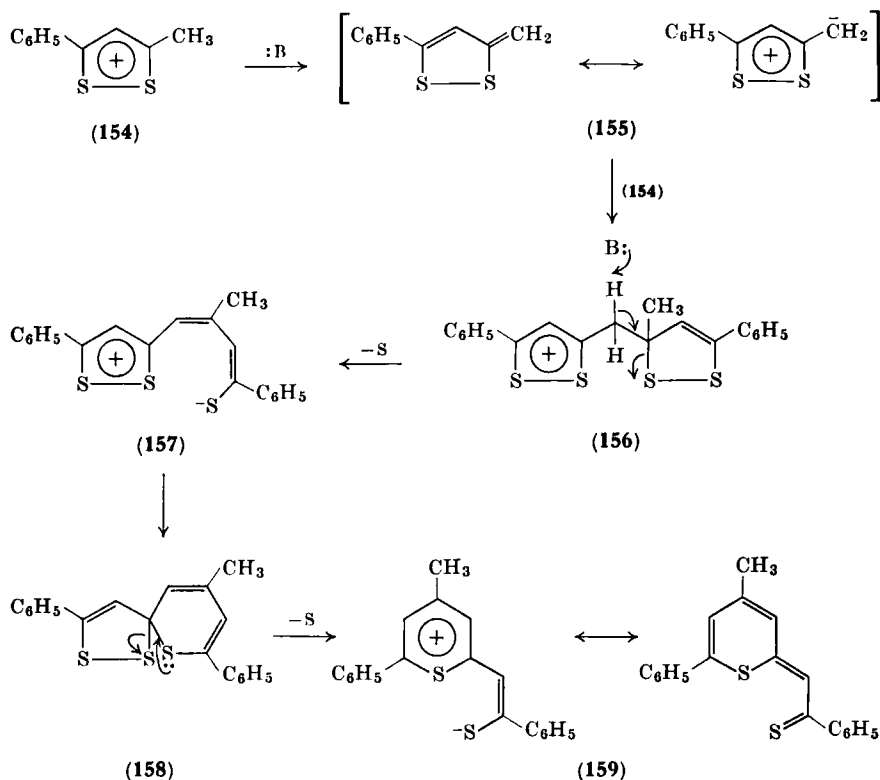
Thus the 1,2-dithiafulvene (**155**) liberated from the 3-methyl-5-phenyl-1,2-dithiolium salt (**154**) by ammonia is unstable, and could not be characterized even in solution. It is doubtful whether **155** can in fact be obtained by this method, since **154** reacts even with the weak base pyridine to yield a product which has been assumed to possess the structure **159**. The formation of this product has been plausibly explained by the reaction sequence shown in Scheme 9.<sup>119</sup>

The attack of the "acid" (**154**) on the readily polarizable 1,2-dithiafulvene (**155**) corresponds to the extremely ready addition of electrophilic reagents to the simple<sup>71</sup> and vinylogous<sup>74</sup> heptafulvene derivatives, which are iso- $\pi$ -electronic with **155**. The opening of the dithiole rings in **156** and **158** under the pressure of the carbanionoid electron pair liberated by the proton abstraction and of the free electron pair on the sulfur, as well as the elimination of elementary sulfur and the intramolecular electrophilic attack of the mercaptide ion (**157**) on the 5-position to form **158**, are simply the typical reactions of 1,2-dithioles that have already been discussed (Section II, B, 3). The reactivity of the 3-methyl group in **154** finds many parallels in the ease of condensation of the methyl-substituted pyridinium,<sup>92</sup> pyrylium,<sup>91</sup> thiopyrylium,<sup>93</sup> and tropylium<sup>120</sup> salts, and particularly

<sup>119</sup> D. Leaver, Personal communication (1964).

<sup>120</sup> K. Hafner, H. W. Riedel, and M. Danielisz, *Angew. Chem.* **75**, 344 (1963).

in the numerous earlier reactions of the 5-methyl group in the trithiones.<sup>121</sup> Whereas the condensation requires basic catalysts in the case of the "trithiones," however, the 3-methyl-1,2-dithiolium salts condense with aldehydes in the absence of catalysts. This is due to



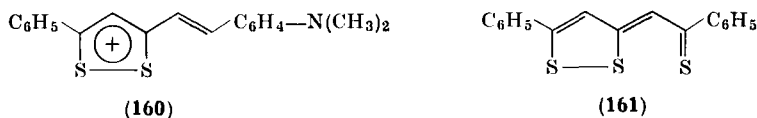
SCHEME 9

the even higher acidity of the C—H bond in these compounds, and is the ultimate reason for the failure of the base-catalyzed autocondensations of Scheme 9 to occur in this case. Thus 3-methyl-5-phenyl-1,2-dithiolium perchlorate (154) reacts smoothly with *p*-dimethylaminobenzaldehyde to form the styryl-substituted salt (160),<sup>14a</sup> and with methyl dithiobenzoate to form "thiophiophene" (161).<sup>101</sup>

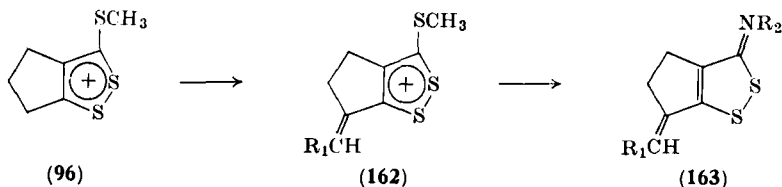
Another similar example is the condensation of "trithionium salts" of the type 96 with aldehydes in glacial acetic acid. This reaction,

<sup>121</sup> H. Quiniou and N. Lozac'h, *Bull. Soc. Chim. France* p. 517 (1958).

unlike that of the corresponding "trithiones," again proceeds without basic catalysts, and leads to the formation of a series of intensely



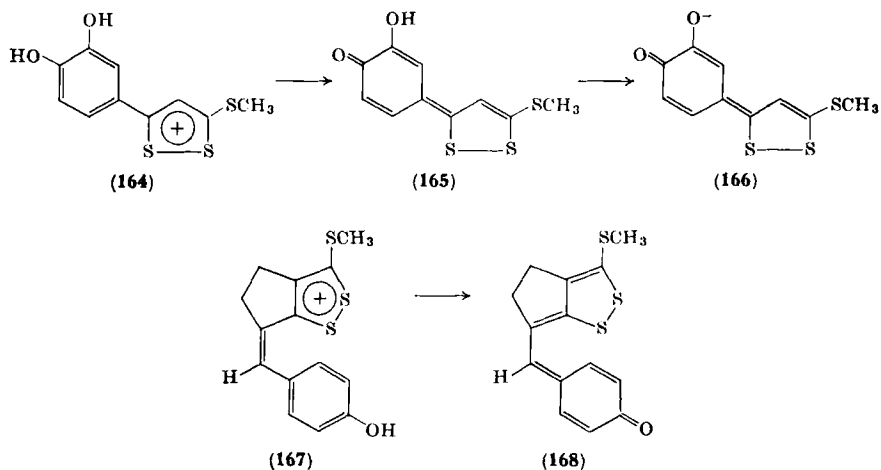
colored "trithionium salts" (162); these react further with primary amines to yield cyanine dyes of the type 163.<sup>59</sup>



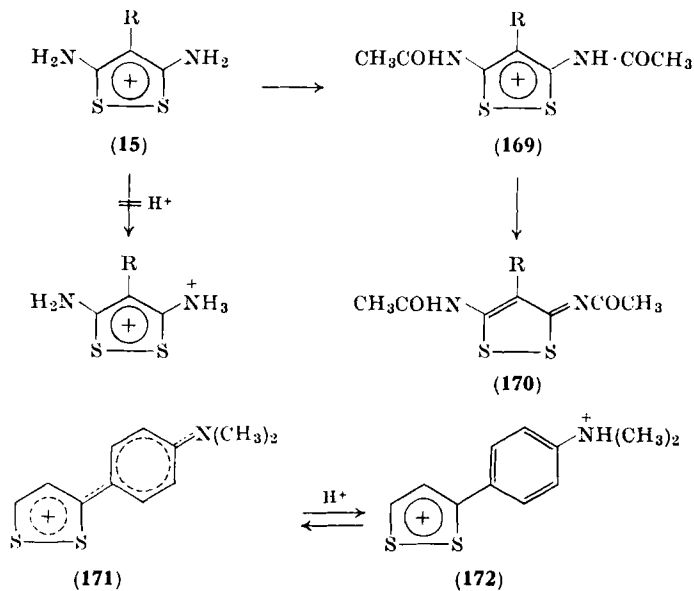
This method of preparing cyanine-like dyes is more versatile than the basically comparable methods previously known. Both the carbonyl components and the bases can be varied within wide limits.

According to NMR measurements, the dissolution of "Baumann-Fromm disulfides" in strong acids (e.g., trifluoroacetic acid) is accompanied by protonation of the exocyclic oxygen atom (Section II, A, 2, c). Water is sufficiently basic to liberate the bases from these strongly acidic "3-hydroxy-1,2-dithiolium salts."<sup>52, 53</sup> The salts 164 and 167 are also vinylogous acids of the "Baumann-Fromm disulfides" with indicator properties. In neutral and alkaline media they are capable of splitting off one and two protons, respectively, with formation of the (sometimes unstable) quinoid compounds 165, 166, and 168.<sup>58, 59</sup>

The 3-mercapto-1,2-dithiolium salts (39a) also suffer deprotonation on addition of water. This behavior is the basis of a simple and effective method of purification, which is particularly useful for aryl-substituted "trithiones."<sup>46</sup> The tendency towards charge neutralization in the alkylmercapto-1,2-dithiolium ions is also the reason for the relative ease of removal of the alkyl group (cf. thermal dealkylation, transmethylation), as well as for the extremely labile bonding of other groups such as acyl—, —SO<sub>2</sub>—, —SO—, —S<sub>2</sub>Cl, and halogen to the exocyclic S atom of the corresponding 3-mercapto-1,2-dithiolium derivatives.



“3,5-Diamino-1,2-dithiolium salts” (15) can easily be converted into the corresponding *N,N'*-diacetyl salts (169).<sup>9</sup> The N—H bonds in 169 possess considerable acidity, and the reaction of these salts with ammonia leads to the stable bases 170. This agrees with the facts that, according to NMR studies, 15 cannot be protonated with  $\text{CF}_3\text{CO}_2\text{H}$ ,



for example, and that the protonation of the 3-(*p*-dimethylamino-phenyl)-1,2-dithiolium ion (**171**) to yield **172** becomes practically quantitative only in solvents with very high proton activities.<sup>45</sup>

### C. PHYSICAL PROPERTIES

#### 1. *Quantum Mechanical Calculations*

The methods and problems of quantum mechanical calculations on the electronic structures of *S*-heterocyclic compounds in general, and of the 1,2- and 1,3-dithiolium ions in particular, have already been discussed in detail by Zahradnik in Volume 5 of this series.<sup>1</sup> We can therefore confine the present discussion to the essential conclusions drawn from these theoretical studies. It should, however, be pointed out that, insofar as they relate to the 1,2-dithiolium ion, these are largely a priori calculations.

Zahradnik's molecular diagrams a-d (Fig. 1)<sup>122</sup> are based on a simple Hückel LCAO MO treatment, first including the *d* orbitals of the two-ring sulfur atoms (model A), and then neglecting any participation of the *d* orbitals (model B). In all four diagrams, C-3 has a lower electron density and a greater "free valence" than C-4. This charge distribution is not fundamentally changed by variation of the resonance integral  $\beta_{ss}$ . Further calculations showed that variation of the  $\beta_{cs}$  resonance integral within the limits 0.6–1.0 also causes no appreciable change in the relative charge densities. In all four diagrams the C—C bond order is evidently much higher than the C—S bond order.

Bergson<sup>123</sup> obtained markedly different results, particularly in relation to the bond orders. In diagrams e and f (Fig. 1), which are based on an SCF LCAO MO method, a considerably greater double-bond character is attributed to the C—S bond in comparison with the C—C bond. This fact and the high bond order of the S—S bond lead to a picture of cyclic delocalization of the  $\pi$  electrons with participation of the S—S bond. On the basis of this purely physical criterion, therefore, the 1,2-dithiolium ion appears to be a typical "aromatic" ion.

Translated into valence-bond terms, this would mean that a certain importance must be assigned to the decet configuration

<sup>122</sup> R. Zahradnik and J. Koutecky, *Collection Czech. Chem. Commun.* **28**, 1117 (1963).

<sup>123</sup> G. Bergson, *Arkiv Kemi* **19**, 181 (1962).

(176) in representing the resonance hybrid of the 1,2-dithiolium ion. However, the calculated bond orders and relative electron densities

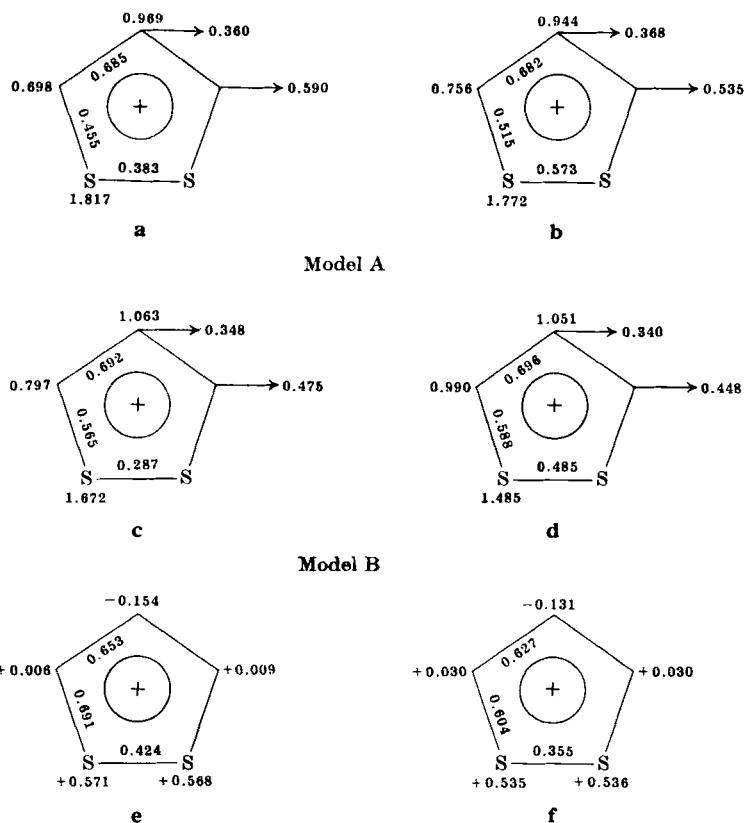
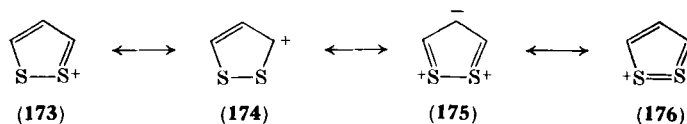


FIG. 1. Molecular diagrams of the 1,2-dithiolium cation.<sup>122,123</sup> Model A: **a**,  $\beta_{ss} = 0.5\beta$ ; **b**,  $\beta_{ss} = 1.0\beta$ . Model B: **c**,  $\beta_{ss} = 0.5\beta$ ; **d**,  $\beta_{ss} = 1.0\beta$ . (Relative electron densities, bond orders, and free valences.) **e**, "the nonoverlap case"; **f**, "the overlap case." (Relative electron densities and bond orders.)

indicated in diagrams **e** and **f** were discussed only for the resonance structures 173–175, the greatest importance being attributed to the sulfonium structures (173).



Calculations by Zahradnik and Koutecky<sup>122</sup> on the basis of model A (see above) gave a qualitatively identical picture for "trithione" (177) and the two other 1,2-dithiolium derivatives (178 and 179) (Fig. 2). The C-4—C-5 bond in all the diagrams, with a bond order of approximately 0.8, approximates to a double bond.

Bergson has also calculated the electronic structure of the "trithione" molecule using the above approximations. A very close agreement was found between the calculated bond lengths and those found experimentally by X-ray analysis of "4-methyltrithione."<sup>124</sup> Even in this case, however, there is some controversy regarding the significance of the calculated S—S bond order (0.243) as a measure of the participation of the S—S bond in the mesomeric system. The measured deviation (0.04 Å) of the S—S bond length from the

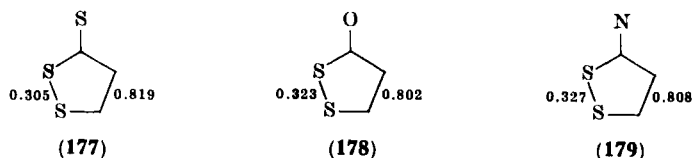


FIG. 2. S—S and C-4—C-5 bond orders (Model A) of 1,2-dithiol-3-thione, 1,2-dithiol-3-thione, and 1,2-dithiol-3-imine.

"normal" value (2.08 Å)<sup>125</sup> has in any case been interpreted as indicating that the disulfide bond takes no part in the mesomeric  $\pi$ -electron system of this planar "trithione" molecule.

On the assumption that the chemical reactivity of the 1,2-dithiolium ion is mainly determined by the charge distribution in the ground state, nucleophilic or free-radical attack is assumed to take place only on C-3; the positive ion should be stable towards electrophilic reagents. In view of the practical investigations discussed in Section II, B, most of which were carried out after the theoretical work, the first assumption appears to be only partly correct, since nucleophilic attack on the disulfide bridge has also been observed in some cases. This argument may not, however, be absolutely sound, since the assumptions on which the theory is based refer only to the parent system, whereas the experimental work in which attack on the disulfide bond occurred was carried out on substituted 1,2-dithiolium compounds.

<sup>124</sup> W. L. Kehl and G. A. Jeffrey, *Acta Cryst.* **11**, 813 (1958).

<sup>125</sup> S. C. Abrahams, *Quart. Rev. (London)* **10**, 407 (1956).

If the maxima of the longest-wave absorption bands of a number of substituted 1,2-dithiolium salts are plotted against the transition energies  $E(N-V')$  calculated by Zahradnik, the points all fall on a straight line.<sup>1</sup>

In connection with the charge distribution in the 1,2-dithiolium ion, it may be of interest that, according to quantum mechanical calculations, the electron density on C-3 of the 1,2-dithioly radical (seven  $\pi$  electrons) is higher than that on C-4.<sup>122</sup>

## 2. Molecular Structure

X-ray diagrams for a number of substituted 1,2-dithiolium salts have been obtained by the oscillating crystal method and by the Weissenberg method, using the  $\text{CuK}_\alpha$  ( $\lambda = 1.543 \text{ \AA}$ ) radiation. These

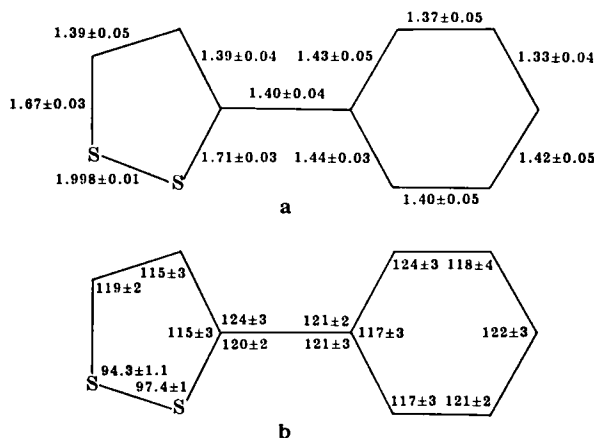


FIG. 3. (a) Bond lengths ( $\text{\AA}$ ) and (b) bond angles ( $^\circ$ ) in the 3-phenyl-1,2-dithiolium ion.

diagrams were then used to find the dimensions of the unit cell.<sup>126a</sup> The refined crystal and molecular structure of 3-phenyl-1,2-dithiolium iodide will be published by Hordvik and Kj ge.<sup>126b</sup>

All bond lengths found for the planar 1,2-dithiolium ring (Fig. 3) are significantly shorter than single bonds and it may be concluded that the 1,2-dithiolium ring is stabilized through  $\pi$ -orbital delocalization. The bond orders estimated assuming linear bond-order/bond-length relations and using accepted values for the lengths of S—S and

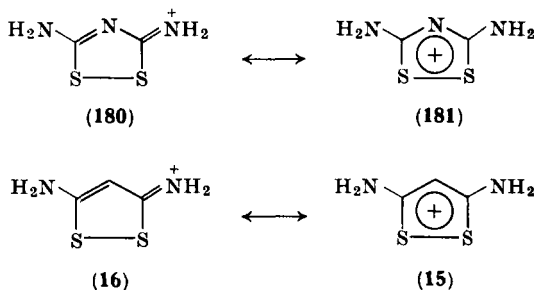
<sup>126a</sup> A. Hordvik, *Acta Chem. Scand.* **17**, 1809 (1963).

<sup>126b</sup> A. Hordvik and H. M. Kj ge, *Acta Chem. Scand.* (in press).



C—S single and double bonds agree with those calculated by Bergson [the  $\pi$ -bond orders of the S—S bonds in Fig. 1e and f (0.35–0.42) correspond to a bond length of 2.01–2.00 Å; cf. preceding section]. The angle between the plane of the benzene ring and that of the 1,2-dithiolium ring is 27°. Unpublished crystal structure analyses of the 4-phenyl-1,2-dithiolium iodide<sup>126c</sup> and bromide<sup>126c</sup> also show good agreement between calculated bond orders and measured bond lengths.

The S—S bond lengths on the other hand in 3,5-diamino-1,2-dithiolium iodide (**16**,  $2.09 \pm 0.02$  Å)<sup>126d</sup> and in the isomorphous thiuret hydroiodide (**180**,  $2.083 \pm 0.015$  Å)<sup>16, 126e</sup> indicate—in accord with earlier ideas of Foss and Tjomsland<sup>16</sup>—that the conjugation in these compounds does not extend over the S—S bond. It has been concluded from structural investigations of thiuret hydrobromide and



hydrochloride<sup>126e</sup> that the proximity of the iodide ion to the disulfide bridge in **16** and **180** affects the S—S bond only to a very small degree. The relative weight of resonance forms containing S—S double bonds should thus be smaller in the “3,5-diamino-1,2-dithiolium ion” than in the unsubstituted 1,2-dithiolium ion. The character of the former as an iminium ion with the positive charge largely localized on the exocyclic substituents is further substantiated by NMR data. Further support for the reduction of the  $\pi$ -bond order of the S—S bond, and probably also of the S—C bond, in the diamino derivative (**15**) relative to the corresponding bond orders in the unsubstituted ion,

<sup>126c</sup> A. Hordvik, S. Joys, J. Sundsfjord, and S. Sletten, To be published.

<sup>126d</sup> A. Hordvik, *Acta Chem. Scand.* **19**, 1039 (1965).

<sup>126e</sup> A. Hordvik and J. Sundsfjord, *Acta. Chem. Scand.* **19**, 753 (1965); A. Hordvik and S. Joys, *ibid.* **19**, 1539 (1965).

is derived from X-ray data on rhodan hydrate<sup>126f</sup> (a), xanthan hydrate<sup>126g</sup> (b), and "4-methyltrithione" (c) (Fig. 4). Clearly, the S—S bond in (c) is shorter than in (a) and (b). The difference is small, but in the right direction. The S<sub>1</sub>—C<sub>1</sub> bonds in (a) and (b) are both longer than the equivalent bond in (c) by three times the respective standard deviations. Apparently  $\pi$ -bonding between C<sub>1</sub> and the amino nitrogen occurs at the expense of the C<sub>1</sub>—S<sub>1</sub>  $\pi$  bonding.

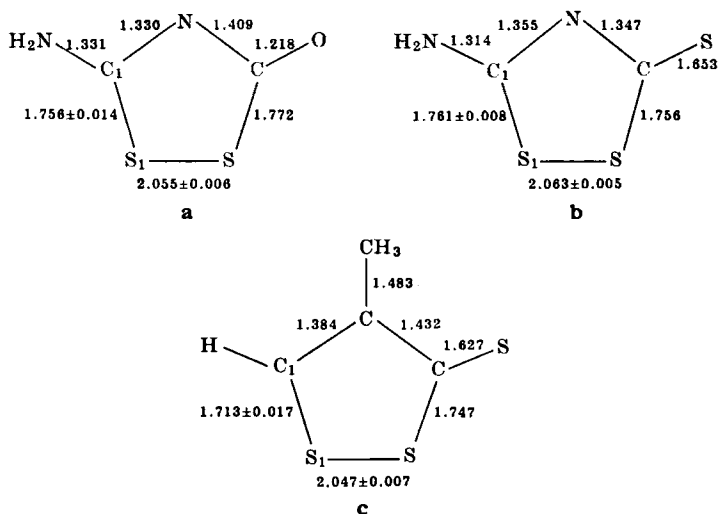


FIG. 4. Bond lengths (Å) in rhodan hydrate (a), xanthan hydrate (b), and "4-methyltrithione" (c).

Preliminary results<sup>126h</sup> of a complete structure determination of 3,5-diacetamino-1,2-dithiolium iodide (**169**) indicate partial bonding between sulfur and oxygen leading to a shortening of the S—S bond, a fact which brings to mind the partial S—O bond in the 2,5-dimethyldithiofurophthene<sup>110</sup> and the equal bond length of the two S—S bonds in "thiothiophene."<sup>110, 126i</sup>

### 3. IR and Electronic Absorption Data

The energy of the S—S stretching vibration is of extreme interest in connection with the controversial S—S bond character in the

<sup>126f</sup> A. Hordvik, *Acta Chem. Scand.* **14**, 1218 (1960).

<sup>126g</sup> A. Hordvik, *Acta Chem. Scand.* **15**, 1186 (1961); **17**, 2575 (1963).

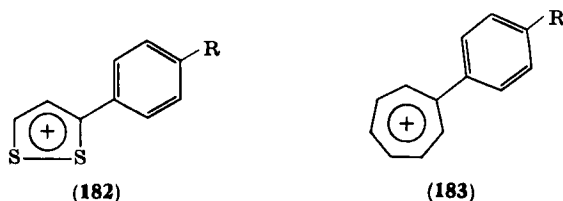
<sup>126h</sup> A. Hordvik and H. M. Kj ge, *Acta Chem. Scand.* **19**, 523 (1965).

<sup>126i</sup> A. Hordvik, *Acta Chem. Scand.* **19**, 1253 (1965).

1,2-dithiolium system. However, no comprehensive and reliable interpretation of the IR spectra of even the simplest 1,2-dithiolium derivatives has yet been advanced. The difficulties that stand in the way of a definite assignment of the S—S stretching band in unsaturated cyclic disulfides were pointed out some time ago by Schotte.<sup>127</sup>

The available information on the absorption maxima in the electronic spectra of 1,2-dithiolium derivatives is listed in Table VIII.

The spectrum of the parent system (No. 1) is made up of two intense structureless bands, the longer-wave maximum exhibiting only slight solvatochromism.<sup>45</sup> A particularly interesting point, in view of the close theoretical relationship between the 1,2-dithiolium ion and the tropylium ion, is the similar absorption behavior of 3-phenyl-1,2-dithiolium (**182**) and phenyltropylium (**183**) ions.<sup>128</sup>



	R	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$
<b>a</b>	H	356	19,000	369	15,200
<b>b</b>	OCH <sub>3</sub>	432	19,500	435	22,400
<b>c</b>	N(CH <sub>3</sub> ) <sub>2</sub>	535	39,000	569	36,400

The long-wave bands of **182a** and **183a** (which are probably due, as in the azulonium ion,<sup>129</sup> for example, to electron transfer from the phenyl group to the 1,2-dithiolium or tropylium ion) are very similar in position and maximum extinction; they suffer bathochromic shifts of similar magnitudes when identical donor substituents such as OCH<sub>3</sub> or N(CH<sub>3</sub>)<sub>2</sub> are introduced into the *p*-positions of the phenyl groups, with a consequent increase in the probability of electron transfer.

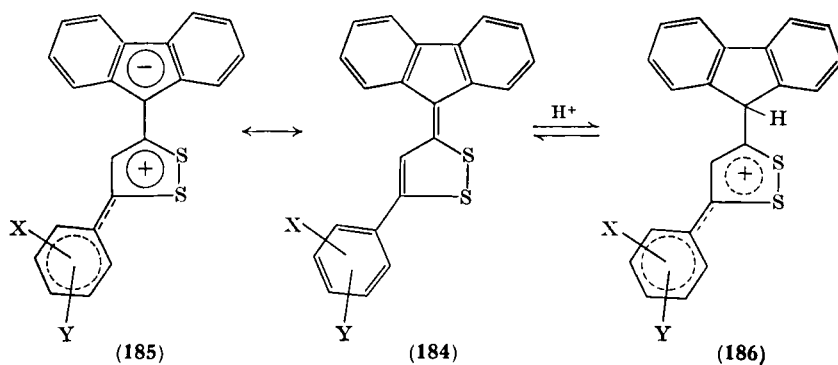
Zahradnik<sup>1</sup> has already pointed out that it is not yet possible to

<sup>127</sup> L. Schotte, *Arkiv Kemi* **9**, 441 (1956).

<sup>128</sup> C. Jutz and F. Voithenleitner, *Ber.* **97**, 29 (1964).

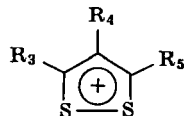
<sup>129</sup> W. Meier, D. Meuche, and E. Heilbronner, *Helv. Chim. Acta* **45**, 2628 (1962).

produce a comprehensive and quantitatively convincing theoretical interpretation. Experimental confirmation has repeatedly been found, however, for the theoretical postulate that electron-donating substituents in the 3- and 5-positions of the dithiolium ring cause a greater bathochromic shift than in the 4-position. This has been explained by the fact that none of the canonical structures given in Section II, C, 1 has a positive charge in the 4-position; consequently a substituent in this position is unlikely to participate in the mesomerism of the heterocyclic ring system. This reasoning implies that the electronic configuration in the excited state is the same as that in the ground state. It is not surprising, therefore, that certain phenomena, such as the considerable red shift of the two maxima in No. 16 on introduction of a  $p$ -NO<sub>2</sub> group (No. 17), and the pronounced red shift of the long-wave maximum in No. 10 with respect to that in No. 9, cannot be explained on the basis of this interpretation.



		CHCl <sub>3</sub>		CF <sub>3</sub> CO <sub>2</sub> H		
X	Y	$\lambda_{\max}(\text{m}\mu)$	$\epsilon$	$\lambda_{\max}(\text{m}\mu)$	$\epsilon$	
<b>a</b>	H	H	470	8,370	369	17,800
<b>b</b>	H	OCH <sub>3</sub> (4)	468	13,200	431	16,780
<b>c</b>	H	N(CH <sub>3</sub> ) <sub>2</sub> (4)	466	65,400		
<b>d</b>	H	OH(4)	464		417	498 in NaOH
<b>e</b>	(OCH <sub>3</sub> )(3)	(OCH <sub>3</sub> )(4)	468	22,100	444	23,400
<b>f</b>	(OCH <sub>3</sub> )(2)	(OCH <sub>3</sub> )(4)	487	21,100	432	28,600
<b>g</b>	(OCH <sub>3</sub> )(2)	(OCH <sub>3</sub> )(5)	488	17,000	448	8,625

TABLE VIII  
ELECTRONIC ABSORPTION DATA OF 1,2-DITHIOLIUM SALTS



No.	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	Solvent	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	Reference
1	H	H	H	CH <sub>3</sub> CN	242; 285	4,250; 4,350	<i>a</i>
2	Cl	H	H	70% HClO <sub>4</sub>	262; 300	3,900; 5,620	<i>b</i>
3	C <sub>6</sub> H <sub>5</sub>	H	H	0.1 N HCl	287; 356	3,800; 19,000	<i>c</i>
4	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	H	CF <sub>3</sub> CO <sub>2</sub> H	261; 312; 432	4,580; 915; 19,500	<i>d</i>
5	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	H	0.1 N HCl	535	39,000	<i>e</i>
6	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	H	0.1 N HCl/ C <sub>2</sub> H <sub>5</sub> OH	260; 340	8,400; 14,200	<i>c</i>
7	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (3)	H	H	0.1 N HCl/ C <sub>2</sub> H <sub>5</sub> OH	250; 337	12,700; 13,300	<i>c</i>
8	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (3,4)	H	H	CF <sub>3</sub> CO <sub>2</sub> H	260; 357; 443	6,650; 4,380; 16,000	<i>a</i>
9	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,4)	H	H	CF <sub>3</sub> CO <sub>2</sub> H	274; 352; 429	5,880; 4,500; 31,000	<i>a</i>
10	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,5)	H	H	CF <sub>3</sub> CO <sub>2</sub> H	281; 347; 453	4,760; 4,450; 4,920	<i>a</i>
11	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	HClO <sub>4</sub> / C <sub>2</sub> H <sub>5</sub> OH	219; 295; 354	7,700; 6,900; 22,400	<i>f</i>
12	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	HClO <sub>4</sub> / C <sub>2</sub> H <sub>5</sub> OH	233; 381	10,300; 17,300	<i>f</i>

13	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	H	$\text{C}_6\text{H}_5$	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	557	38,000	e
14	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	H	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	495; 588	22,000; 93,000	e
15	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	586	64,000	e
16	H	$\text{C}_6\text{H}_5$	H	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	242; 345	21,500; 1,400	c
17	H	$\text{C}_6\text{H}_4\text{—NO}_2$ (4)	H	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	267; 385	10,400; 7,960	c
18	H	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	544		e
19	H	$\text{C}_6\text{H}_4\text{—NO}_2$ (4)	$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	545		e
20	$\text{—C}_4\text{H}_4\text{—}$		H	$\text{CF}_3\text{CO}_2\text{H}$	317; 389	8,400; 2,150	a, g
21	$\text{—C}_4\text{H}_4\text{—}$		$\text{C}_6\text{H}_4\text{—N(CH}_3)_2$ (4)	0.1 N HCl/ $\text{C}_2\text{H}_5\text{OH}$	588	29,000	e
22	$\text{—C}_4\text{H}_4\text{—}$		Fluorenyl	$\text{CF}_3\text{CO}_2\text{H}$	262; 316; 394	16,800; 9,360; 3,350	a

<sup>a</sup> E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

<sup>b</sup> J. Faust, Dissertation, Dresden (1964).

<sup>c</sup> E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961).

<sup>d</sup> A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Tetrahedron Letters* **19**, 1209 (1963).

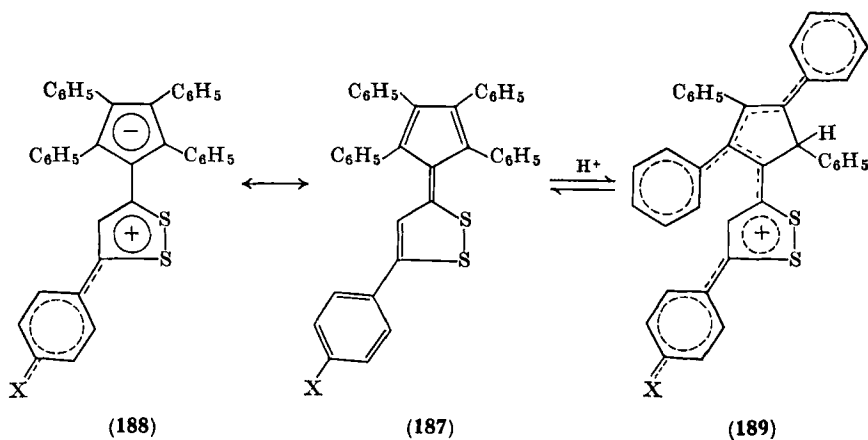
<sup>e</sup> E. Klingsberg and A. M. Schreiber, *J. Am. Chem. Soc.* **84**, 2941 (1962).

<sup>f</sup> D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.* p. 5104 (1962).

<sup>g</sup> A. Lüttringhaus, M. Mohr, and N. Engelhard, *Ann.* **661**, 84 (1963).

The longer-wave maxima (corresponding to an  $N-V'$  transition) of the 1,2-dithiolium salts obtained by protonation of the 1,2-dithiafulvalenes (**184**) are affected by substitution in the phenyl residue to the same extent as those of the similarly substituted simple derivatives in Table VIII (Nos. 3–10).<sup>45</sup>

The longer-wave maxima of the corresponding bases, on the other hand, are practically independent of these substituents. The same is true of the base-acid pair **187** and **189**. The relatively small red shift on replacement of H by  $\text{OCH}_3$  or  $\text{N}(\text{CH}_3)_2$  in the salts (**189**) has been explained by delocalization of the positive charge as shown (i.e., over the homocyclic ring and the attached phenyl groups), with a consequent decrease in the positive charge on C-5, and hence a weakening of the interaction with the substituents in this position in the ground and excited states. The fact that the  $N-V'$  transitions of all the bases **184**, **187**, and **190** are largely unaffected by the substitution of the phenyl ring is regarded as evidence that the individual



	X	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$
a	H	512	15,100 <sup>a</sup>	552	16,500 <sup>b</sup>
b	$\text{OCH}_3$	512	25,100 <sup>a</sup>	548	29,900 <sup>b</sup>
c	$\text{N}(\text{CH}_3)_2$	532	25,000 <sup>a</sup>	595	25,000 <sup>c</sup>
d	$\text{NH}(\text{CH}_3)_2$	502	10,300 <sup>c</sup>	550	16,600 <sup>d</sup>

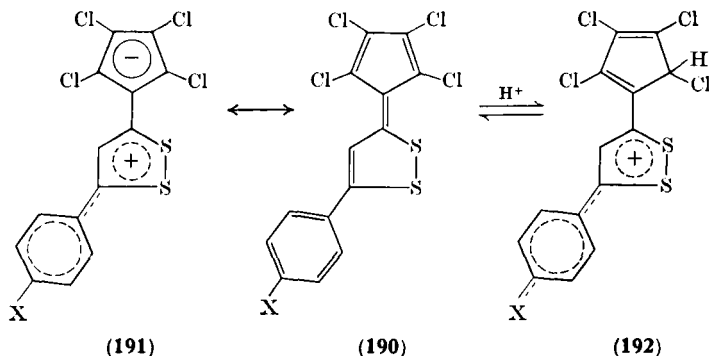
<sup>a</sup>  $\text{CHCl}_3$

<sup>b</sup>  $\text{CF}_3\text{CO}_2\text{H}$

<sup>c</sup> 5%  $\text{HClO}_4/\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O}$

<sup>d</sup> 30%  $\text{HClO}_4/\text{C}_2\text{H}_5\text{OH}/\text{H}_2\text{O}$

bonds in this cross-conjugated bond system are largely localized (in agreement with the findings for the iso- $\pi$ -electronic sesquifulvalenes), and that the dipolar limiting structures **185**, **188**, and **191** should have modest weights only in describing the electronic ground state.



		CHCl <sub>3</sub>		CF <sub>3</sub> CO <sub>2</sub> H	
	X	$\lambda_{\max}(\text{m}\mu)$	$\epsilon$	$\lambda_{\max}(\text{m}\mu)$	$\epsilon$
a	H	492	14,400	454	29,800
b	OCH <sub>3</sub>	498	20,650	479	26,250

#### 4. NMR Data

The literature at present contains very few NMR data for 1,2-dithiolium salts. The results of systematic NMR studies on a number of 1,2-dithiolium salts and on many "Baumann-Fromm disulfides" and "trithiones" are presented in a Dissertation by Dr. E. Futterer (Freiburg-im-Breisgau, 1964). Most of the data in the following tables were taken from this dissertation.

The magnetic equivalence of H-3 and H-5 in the unsubstituted ion (**193**) (No. 1, Table IX) and in the 4-phenyl derivative (**194**) (No. 7,

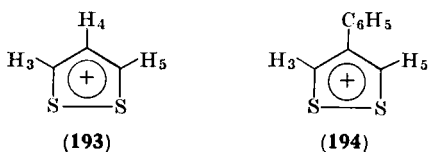




TABLE IX  
CHEMICAL SHIFTS OF 3-SUBSTITUTED 1,2-DITHIOLIUM SALTS<sup>a</sup>

No.	R <sub>3</sub>	δH-5 <sup>b</sup>	δH-4 <sup>b</sup>	Reference
1	H	-0.57 ( <i>D</i> , 5.0)	+1.12 ( <i>D</i> , 5.0)	<i>c</i>
2	C(CH <sub>3</sub> ) <sub>3</sub>	-0.32 ( <i>D</i> , 5.4)	+1.32 ( <i>D</i> , 5.4)	<i>c</i>
3	Cl	-0.43 ( <i>D</i> , 5.0)	+1.46 ( <i>D</i> , 5.0)	<i>d</i>
4	C <sub>6</sub> H <sub>5</sub>	-0.30 ( <i>D</i> , 5.5)	+1.08 ( <i>D</i> , 5.5)	<i>c</i>
5	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	+0.01 ( <i>D</i> , 5.5)	+1.20 ( <i>D</i> , 5.5)	<i>c</i>
6	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (3,4)	-0.13 ( <i>D</i> , 5.5)	+1.18 ( <i>D</i> , 5.5)	<i>c</i>

<sup>a</sup> Ca. 10% solutions in trifluoroacetic acid.

<sup>b</sup> In τ units (TMS = 10); in parentheses multiplicity and coupling constants (cps).

<sup>c</sup> E. Futterer, Dissertation, Freiburg-im-Breisgau (1964).

<sup>d</sup> J. Faust, Dissertation, Dresden (1964).

Table X) has been considered as evidence that the charge distribution in these ions is symmetrical.<sup>43</sup>

The chemical shifts listed in Tables IX to XII, while providing evidence for the existence of the corresponding dithiolium derivatives,

TABLE X  
CHEMICAL SHIFTS OF MONOARYL-SUBSTITUTED 1,2-DITHIOLIUM SALTS<sup>a, b</sup>

No.	R <sub>3</sub>	R <sub>4</sub>	δH-5 <sup>c</sup>	δH-4 <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub>	H	-5.36 ( <i>D</i> , 6.0)	-3.91 ( <i>D</i> , 6.0)
2	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	-5.17 ( <i>D</i> , 5.0)	-3.70 ( <i>D</i> , 5.0)
3	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	-4.47 ( <i>D</i> , 6.0)	-3.27 ( <i>D</i> , 6.0)
4	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,4)	H	-4.93 ( <i>D</i> , 5.5)	-3.67 ( <i>D</i> , 5.5)
5	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,5)	H	-5.15 ( <i>D</i> , 6.0)	-3.85 ( <i>D</i> , 6.0)
6	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (3,4)	H	-5.25 ( <i>D</i> , 5.8)	-3.92 ( <i>D</i> , 5.5)
7	H	C <sub>6</sub> H <sub>5</sub>	-5.62 ( <i>S</i> )	—

<sup>a</sup> Data are taken from the Dissertation of E. Futterer, Freiburg-im-Breisgau (1964).

<sup>b</sup> Ca. 10% solutions in D<sub>2</sub>O.

<sup>c</sup> In ppm units, referred to HDO; in parentheses multiplicity and coupling constants (cps).

were also correlated with the electronic character of the substituents present and with the  $\pi$ -electron densities in the various ring positions. This correlation is naturally valid only where the differences in the

TABLE XI  
CHEMICAL SHIFTS OF DISUBSTITUTED 1,2-DITHIOLIUM SALTS<sup>a,b</sup>

No.	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	δH-4 <sup>c</sup>	δH-5 <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub>	H	Cl	1.32 ( <i>S</i> )	—
2	C(CH <sub>3</sub> ) <sub>3</sub>	H	Fluorenyl	1.27	—
3	C <sub>6</sub> H <sub>5</sub>	H	Fluorenyl	1.17	—
4	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	Fluorenyl	1.32	—
5	C <sub>6</sub> H <sub>3</sub> —(OCH <sub>3</sub> ) <sub>2</sub> (2,5)	H	Fluorenyl	1.06	—
6	C <sub>6</sub> H <sub>5</sub>	H		1.14	—
7	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H		1.26	—
8	C(CH <sub>3</sub> ) <sub>3</sub>	H		2.21	—
9	C <sub>6</sub> H <sub>5</sub>	H		1.91	—
10	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H		2.00	—
11	C <sub>6</sub> H <sub>5</sub>	H	SH	1.74	—
12	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	SH	1.72	—
13	C <sub>6</sub> H <sub>5</sub>	H	SCH <sub>3</sub>	1.65	—
14	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	SCH <sub>3</sub>	1.74	—
15	NH <sub>2</sub>	H	NH <sub>2</sub>	3.48	—
16	C <sub>4</sub> H <sub>8</sub> NO <sup>d</sup>	H	C <sub>4</sub> H <sub>8</sub> NO <sup>d</sup>	3.54	—
17	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	—	−0.06
18	SH	C <sub>6</sub> H <sub>5</sub>	H	—	0.66
19	—C <sub>4</sub> H <sub>4</sub> —		H	—	−1.36 <sup>e</sup>

<sup>a</sup> Data are taken from the Dissertation of E. Futterer, Freiburg-im-Breisgau (1964).

<sup>b</sup> Ca. 10% solutions in trifluoroacetic acid.

<sup>c</sup> In  $\tau$  units (TMS = 10).

<sup>d</sup> *N*-Morpholinyl.

<sup>e</sup> In CF<sub>3</sub>CO<sub>2</sub>D.

chemical shift are entirely attributable to differences in the local  $\pi$ -electron density on the carrier carbon atom. This condition appears to be satisfied at least for the H-5 signals of all the 3-substituted

1,2-dithiolium salts listed in Tables IX and X. Since the point of attachment of the substituents is sufficiently far from the point at which the measurement is to be made, any differences in H-5 should (for a roughly equal effect of a possible but weak ring current) not be due to anisotropy effects, but only to differences in the electron density on C-5.

The site of electrophilic attack on the 1,2-dithiafulvalene derivatives **184**, **187**, and **190** was also determined from the NMR data listed in Table XI.

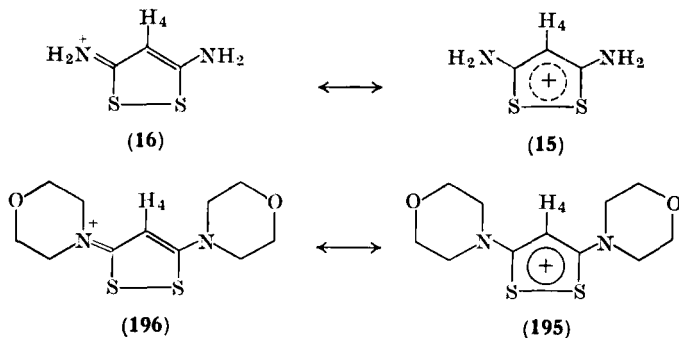
The very close agreement between the  $\delta H$ -4 values for the conjugate acids of **184** (Nos. 2, 3, and 4 in Table XI) and the  $\delta H$ -4 values of the 1,2-dithiolium salts with similar substituents in position 3 (Nos. 2, 4, and 5 in Table IX) confirms that the conjugate acids of **184** have the structure **186**. The marked diamagnetic shift of the H-4 signals of the tetraphenyl salts (**189**) with similar substitution of the heterocyclic ring (Nos. 8, 9, and 10 in Table XI) can only be explained by 5-protonation of **187** to give **189**. The distribution of the positive charge over the homocyclic five-membered ring and the attached groups causes a decrease in the charge on C-4 and a corresponding increase in the screening effect.

In the case of the tetrachloro-1,2-dithiafulvalenes (**190**), the electronic spectra indicate that protonation must again take place in the 5-position. The fact that the H-4 signal (Nos. 6 and 7 in Table XI) appears at such low fields as to suggest at first glance that the protonation occurs in the 9-position is mainly attributed to the deshielding anisotropy effect of the chlorine atom on C-5.

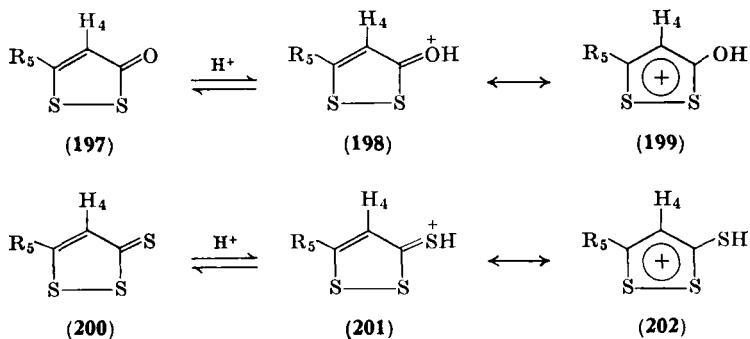
The very high  $\tau$  values for H-4 in the 3,5-diamino (**15**) and dimorpholino (**195**) derivatives ( $\tau_{H-4} = 3.48$  and  $3.54$ , respectively), in comparison with all the other  $\delta H$ -4 values in Table XI, are regarded as showing that the resonance hybrid of these salts is most closely described by the iminium structures **16** and **196**; i.e., the positive charge is largely localized on the exocyclic nitrogen atoms.

This is also shown by the strong paramagnetic shift of the signals for the methylene protons  $\alpha$  to the nitrogen in the morpholino derivative (**196**): it has admittedly not been definitely decided which of the two  $CH_2$  signals in the spectrum of **196** ( $\tau = 5.97, 6.08$ ) is due to the  $CH_2$  groups adjacent to the nitrogen, but the  $N-CH_2$  signal has in any case been displaced to much lower fields in comparison with the  $N-CH_2$  signal in the morpholine spectrum ( $\tau = 7.17$  in  $CCl_4$ ). This

agrees with the strong withdrawal of electrons owing to the positive charge on the adjacent nitrogen atom.

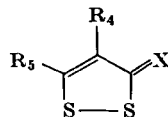


Both the "Baumann-Fromm disulfides" (197) and the "trithiones" (200) are readily protonated in trifluoroacetic acid (Section II, A, 2, c). The chemical shifts of the ring protons of some of these compounds in both carbon disulfide and trifluoroacetic acid are given in Table XII.



The paramagnetic shift of the H-4 signal on passing from carbon disulfide into trifluoroacetic acid is more pronounced for the "trithiones" than for the similarly substituted "Baumann-Fromm disulfides." This has been tentatively accepted as evidence that the importance of the resonance structure 202 in relation to 201 is rather greater than that of 199 in relation to 198, in agreement with the repeated observation that a carbonium center is much more effectively stabilized by an adjacent oxygen than by sulfur.

TABLE XII  
CHEMICAL SHIFTS OF "BAUMANN-FROMM DISULFIDES" (X=O) AND OF "TRITHIONES" (X=S)  
IN CS<sub>2</sub> AND CF<sub>3</sub>CO<sub>2</sub>H<sup>a,b</sup>



No.	R <sub>5</sub>	R <sub>4</sub>	X	CS <sub>2</sub>		CF <sub>3</sub> CO <sub>2</sub> H	
				H-5 <sup>c</sup>	H-4 <sup>c</sup>	H-5 <sup>c</sup>	H-4 <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub>	H	O	—	3.32 ( <i>S</i> )	—	2.75 ( <i>S</i> )
2	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	O	—	3.44 ( <i>S</i> )	—	2.55 ( <i>S</i> )
3	H	C <sub>6</sub> H <sub>5</sub>	O	1.72 ( <i>S</i> )	—	1.53 ( <i>S</i> )	—
4	H	H	S	1.72 ( <i>D</i> , 5.7)	2.98 ( <i>D</i> , 5.7)	0.40 ( <i>D</i> , 5.6)	1.85 ( <i>D</i> , 5.6)
5	CH <sub>3</sub>	H	S	—	3.23 ( <i>Q</i> , 1.5)	—	2.23 ( <i>S</i> )
6	C(CH <sub>3</sub> ) <sub>3</sub>	H	S	—	3.06 ( <i>S</i> )	—	1.87 ( <i>S</i> )
7	C <sub>6</sub> H <sub>5</sub>	H	S	—	2.76 ( <i>S</i> )	—	1.74 ( <i>S</i> )
8	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	S	—	2.85 ( <i>S</i> )	—	1.72 ( <i>S</i> )
9	H	C <sub>6</sub> H <sub>5</sub>	S	1.78 ( <i>S</i> )	—	0.66 ( <i>S</i> )	—

<sup>a</sup> Data are taken from the Dissertation of E. Futterer, Freiburg-im-Breisgau (1964).

<sup>b</sup> Ca. 10% solutions in trifluoroacetic acid.

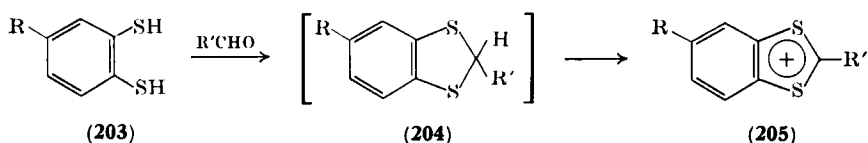
<sup>c</sup> In  $\tau$  units (TMS = 10); in parentheses multiplicity and coupling constants (cps).

### III. The 1,3-Dithiolium Ion

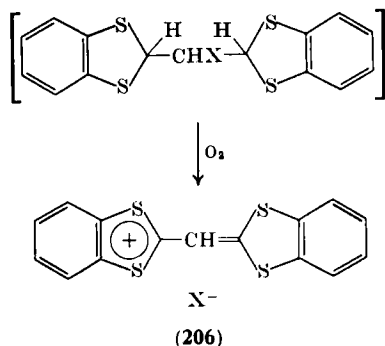
#### A. METHODS OF PREPARATION

##### 1. From Open-Chain Compounds

a. *From cis-Ethylene-1,2-dithiols.* The first 1,3-dithiolium salts to have their structures elucidated were obtained by the acid-catalyzed condensation of benzene-1,2-dithiols (**203**) with aldehydes, followed



by oxidation (without prior isolation) of the resulting benzo-1,3-dithiole derivatives; in accordance with the ideas current at that time, Hurtley and Smiles formulated the end products as sulfonium salts.<sup>4, 130, 131</sup> It has been shown, particularly by Wizinger and Soder<sup>5</sup> that the thermodynamic stabilities of the intermediate 1,3-dithioles (**204**) ultimately depend on the nature of the substituent R'. Typical electron-donating substituents such as OCH<sub>3</sub> or OH groups favor the autoxidation of these cyclic thioacetals to such an extent that they are generally not isolated, but are converted immediately into the ions **205**,<sup>130-132</sup> (Section III, A, 2). The oxidation of the leuco



<sup>130</sup> W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.* p. 534 (1927).

<sup>131</sup> W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.* p. 2263 (1926).

<sup>132</sup> L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1779 (1959).

compounds, which generally proceeds slowly, is then greatly accelerated by the introduction of oxidizing agents such as  $\text{HNO}_3$ , bromine, hydrogen peroxide, benzoquinone, or air<sup>133</sup> (Table XIII). The

TABLE XIII  
ANNELATED 1,3-DITHIOLIUM SALTS (205) FROM  
1,2-BENZENEDITHIOL AND ALDEHYDES

R'	Oxidation agent	X	Reference
$\text{C}_6\text{H}_5$	$\text{HNO}_3$	$\text{NO}_3, \text{HSO}_4$	<i>a</i>
		$\text{Cl}, \text{ClO}_4, \text{PtCl}_6$	<i>a</i>
(2)- $\text{NO}_2\text{—C}_6\text{H}_4$	$\text{Br}_2$	$\text{Br}$	<i>b</i>
(4)- $\text{CH}_3\text{O—C}_6\text{H}_4$	$\text{HNO}_3, \text{H}_2\text{O}_2$ , Quinone	$\text{NO}_3$	<i>b</i>
(4)- $\text{HO—C}_6\text{H}_4$	$\text{HNO}_3$	$\text{NO}_3$	<i>b</i>
(4)- $(\text{CH}_3)_2\text{N—C}_6\text{H}_4$	$\text{H}_2\text{O}_2$ , Quinone	$\text{ClO}_4$	<i>c, d</i>
(2)- $\text{HO—naphthyl-(1)-}$	$\text{Br}_2$	$\text{Br}$	<i>b</i>
$\text{C}_6\text{H}_5\text{—CH=CH—}$	$\text{HNO}_3$	$\text{NO}_3$	<i>b</i>
(4)- $\text{CH}_3\text{O—C}_6\text{H}_4\text{—CH=CH—}$	$\text{H}_2\text{O}_2$ , Quinone, air	$\text{ClO}_4$	<i>b</i>
(4)- $(\text{CH}_3)_2\text{N—C}_6\text{H}_4\text{CH=CH—}$	$\text{H}_2\text{O}_2$ , Quinone, air	$\text{ClO}_4$	<i>c, d</i>

<sup>a</sup> W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.* p. 1821 (1926).

<sup>b</sup> W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.* p. 534 (1927).

<sup>c</sup> L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1779 (1959).

<sup>d</sup> O. Neunhoeffer and A. Nowak, *Naturwiss.* **45**, 491 (1958).

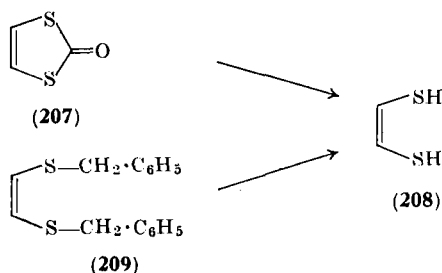
reaction can also be carried out with dialdehydes; thus **203** reacts with chloromalononic or bromomalononic dialdehyde in the presence of air to yield the monomethine salt (**206**).<sup>133</sup>

So far, only fused-ring 1,3-dithiolium salts have been synthesized in this way. The reason for this is that *cis*-ethylene-1,2-dithiols were, until recently, difficult to obtain. Since, however, the *cis*-dithiol (**208**) can now be synthesized by the action of phenyl lithium or sodium alkoxide on "isodithione" (**207**),<sup>134</sup> or by the cleavage of the *cis*-dibenzyl thioether (**209**),<sup>135</sup> simple 1,3-dithiolium salts should now also be readily obtainable by this one-stage method.

<sup>133</sup> O. Neunhoeffer and A. Nowak, *Naturwiss.* **45**, 491 (1958).

<sup>134</sup> R. Mayer and B. Gebhardt, *Ber.* **97**, 1298 (1964).

<sup>135</sup> W. Schroth and J. Peschel, *Chimia (Aarau)* **18**, 171 (1964); W. Schroth, *Tetrahedron Letters* **3**, 195 (1965).



An even simpler route to the fused-ring 1,3-dithiolium salts is by condensation of **203** with aromatic and even aliphatic carboxylic acids.<sup>131, 136, 137</sup> The reaction, which is generally carried out in phosphorus oxychloride, proceeds rapidly and always in good yield. The parent member of this series of benzo-1,3-dithiolium salts is obtained in 80–90% yield when the acid used is formic acid (Table

TABLE XIV  
ANNELATED 1,3-DITHIOLIUM SALTS (**205**) FROM  
4-METHYL-1,2-BENZENEDITHIOL AND CARBOXYLIC ACIDS

R	R'	Yield (%)	Reference
CH <sub>3</sub>	H	80–90	a, b, c
CH <sub>3</sub>	CH <sub>3</sub>	65–70	a, b, c
CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	—	d
CH <sub>3</sub>	(4)-CH <sub>3</sub> O—C <sub>6</sub> H <sub>4</sub> —	—	d
CH <sub>3</sub>	(4)-(CH <sub>3</sub> ) <sub>2</sub> N—C <sub>6</sub> H <sub>4</sub> —	—	c, d
CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> —CH=CH—	—	a, d
CH <sub>3</sub>	(4)-CH <sub>3</sub> O—C <sub>6</sub> H <sub>4</sub> —CH=CH—	—	a, d
CH <sub>3</sub>	(4)-(CH <sub>3</sub> ) <sub>2</sub> N—C <sub>6</sub> H <sub>4</sub> —CH=CH—	—	a

<sup>a</sup> R. Wizinger and L. Soder, *Chimia (Aarau)* **12**, 79 (1958).

<sup>b</sup> L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1733 (1959).

<sup>c</sup> Ciba, British Patent 903,994 (1962); see *Chem. Abstr.* **59**, 7692 (1963).

<sup>d</sup> L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1779 (1959).

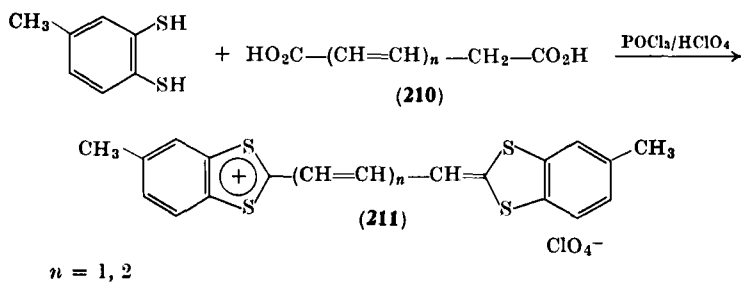
XIV). This reaction also gives good results with unsaturated  $\alpha,\omega$ -dicarboxylic acids having odd carbon chains (**210**).<sup>5, 136, 137</sup> The resulting methine color salts (**211**) are of interest on account of their

<sup>136</sup> L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1733 (1959).

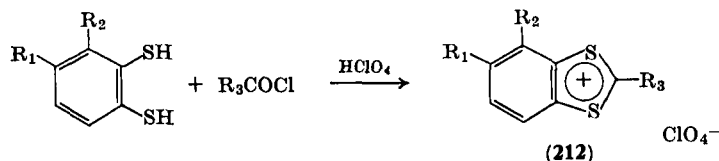
<sup>137</sup> Ciba, British Patent 903,994 (1962); see *Chem. Abstr.* **59**, 7692 (1963).



dyeing properties and because of spectroscopic peculiarities within the homologous series.<sup>138, 139</sup>



Acyl chlorides have also been condensed with various benzene-1,2-dithiols. Very good yields have been obtained in particular in the preparation of 2-methylbenzodithiolium salts (212).<sup>136, 138, 139</sup>



- a:  $\text{R}_1 = \text{R}_2 = \text{H}; \text{R}_3 = \text{CH}_3$   
 b:  $\text{R}_1 = \text{CH}_3; \text{R}_2 = \text{H}; \text{R}_3 = \text{CH}_3$   
 c:  $\text{R}_1 = \text{C}_2\text{H}_5\text{O}; \text{R}_2 = \text{H}; \text{R}_3 = \text{CH}_3$   
 d:  $\text{R}_1/\text{R}_2 = \text{C}_4\text{H}_4; \text{R}_3 = \text{CH}_3$

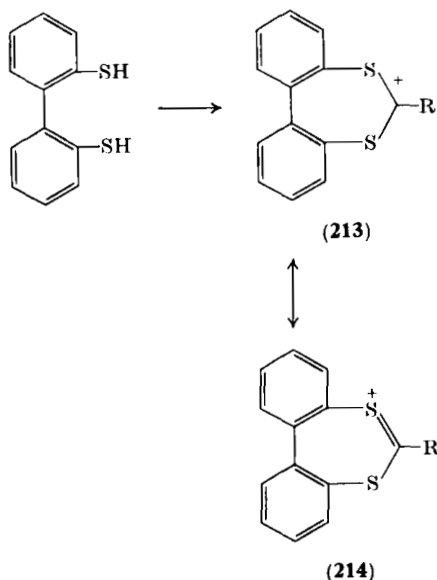
The reaction of orthoformic ester with 1,2-benzenedithiol yields the unsubstituted benzo-1,3-dithiolium cation, which can be isolated as the hexachloroplatinate or as the tetrachlorozincate.<sup>131, 139</sup>

D. Dürr<sup>139</sup> has described attempts to obtain derivatives of the 1,3-dithiepinyl cation (213) (which is a vinylog of 205) by condensing biphenyl-2,2'-dithiol with aldehydes or acyl chlorides under the conditions proposed by Wizinger and Soder.<sup>5</sup> These attempts, however, were completely unsuccessful. If we accept these results as sufficient evidence of the instability of the cation, this instability can be explained by the fact that the seven-membered ring containing

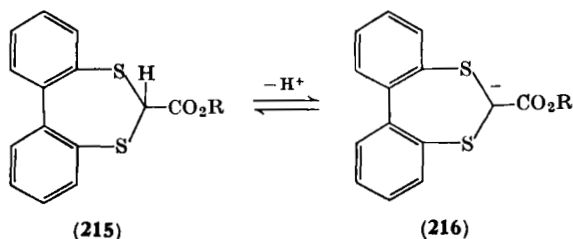
<sup>138</sup> R. Wizinger and D. Dürr, *Helv. Chim. Acta* **46**, 2167 (1963).

<sup>139</sup> D. Dürr, Dissertation, Basel (1961).

two sulfur atoms is almost certainly nonplanar,<sup>140</sup> whereas planarity is a prerequisite for maximum stabilization by delocalization of the sulfur *p* electrons.<sup>141</sup> Little importance should therefore be attached to limiting structures of the type **214**.



Compound **215**, on the other hand, is highly acidic and gives the 1,3-dithiepinyl anion (**216**) even with weak bases. This is not, however,



<sup>140</sup> The 1,4-Dithiadene ring, according to an X-ray analysis exists in a boat form with a C—S—C angle of 100°: W. E. Parham, in "Organic Sulfur Compounds" (N. Kharash, ed.), Vol. 1, Chapter 22. Pergamon Press, Oxford, 1961.

<sup>141</sup> M. M. Kreevoy, *J. Am. Chem. Soc.* **80**, 5543 (1958).

due to any special resonance stabilization by delocalization of the ten-electron  $\pi$  system over the seven-membered ring. According to Breslow,<sup>142</sup> the lack of "aromaticity" in this case is again due to the nonplanar structure.

A very elegant and apparently versatile synthesis of "2-amino-1,3-dithiolium" derivatives (**217**) has recently been published by Addor.<sup>143</sup> In this method, the benzenedithiol (**203**) is reacted with cyanogen chloride in a polar solvent under the catalytic action of acids and alcohol, the presence of the alcohol being essential to the catalytic activity of the acid. This seems unusual, since the reaction of both alkyl and aryl cyanides with mercaptans proceeds rapidly at 0° in the presence of acids, and does not require the assistance of an alcohol.<sup>144</sup>

The reaction sequence on the following page has been proposed as a simplified explanation of the function of the alcohol.

The mechanism outlined here requires that mercaptan should react rapidly with the chloroimidate (**220**) to form **221**, but should not react with the protonated cyanide (**219**); the first of these points is understandable in view of the reactivity of mercaptans towards acyl chlorides or aldehydes and ketones, but there is as yet no satisfactory explanation for the second point.

Cyanogen chloride has so far been reacted, always with very good yields, with a series of ethane-1,2-diols and ethane-1,2-dithiols, as well as with benzene-1,2-dithiol; however, it has not yet been reacted with the simple ethylene-1,2-dithiol, which now offers further preparative possibilities in view of the new syntheses mentioned earlier. Similar 2-amino substituted 1,3-dithiolium derivatives have been synthesized by Sundholm and Smith starting from 2,3-dichloro-1,4-naphthoquinone and dimethylammonium dimethyldithiocarbamate or tetramethylthiuram disulfide.<sup>145</sup>

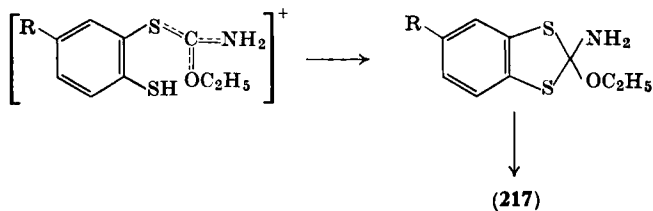
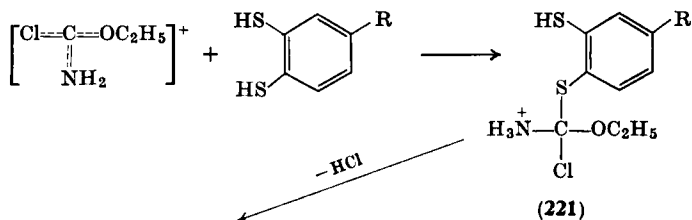
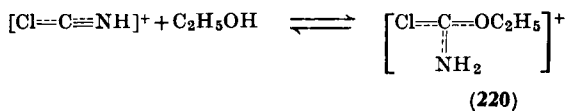
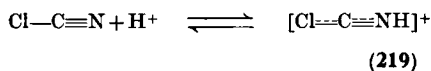
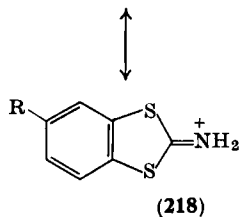
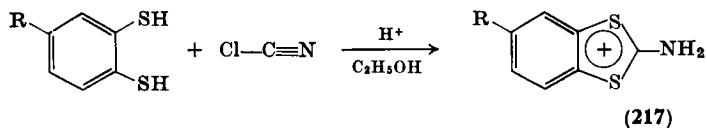
It is easy to see that the true charge distribution in 1,3-dithiolium derivatives with typical electron-donating substituents in position 2 is most closely described by the iminium limiting formula (**218**); Addor accordingly referred to the compounds as hydrochlorides of the 2-imino-1,3-dithiole. The reader is referred back to the similar problem encountered in the cases of the "3,5-diamino-1,2-dithiolium

<sup>142</sup> R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.* **85**, 431 (1963).

<sup>143</sup> R. W. Addor, *J. Org. Chem.* **24**, 738 (1964).

<sup>144</sup> R. Roger and D. G. Neilson, *Chem. Rev.* **61**, 179 (1961).

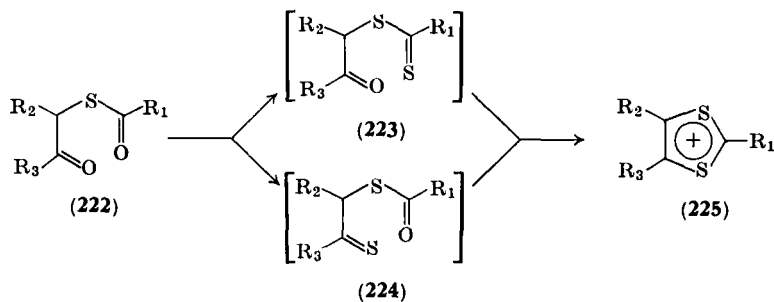
<sup>145</sup> N. K. Sundholm and A. E. Smith, *J. Am. Chem. Soc.* **73**, 3459 (1951).



salts'' (Sections II, A, 1, c and II, C, 4) and the hydrochlorides of the 3-imino-1,2-dithiols (Section II, A, 2, c).

b. *From S- $\alpha$ -Oxoalkyl Thiocarboxylates.* Many alkyl- or aryl-substituted 1,3-dithiolium salts (225) have been obtained by acid-catalyzed cyclization of *S*- $\alpha$ -oxoalkyl thioesters (222) in a mixture of perchloric acid and glacial acetic acid. Under these conditions, the yield of 225 never exceeds 50%, and is generally only a few per cent.

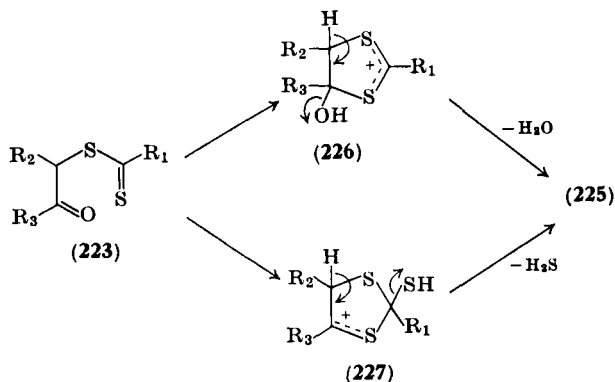
A large part of the compound **(222)** is consumed in converting the remaining monothioester **(222)** into the dithioester. It is not yet clear



- a:  $\text{R}_1 = \text{R}_2 = \text{C}_6\text{H}_5$ ;  $\text{R}_3 = \text{H}$   
b:  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{C}_6\text{H}_5$ ;  $\text{R}_3 = \text{H}$   
c:  $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{C}_6\text{H}_5$

which of the two carbonyl oxygens in **222** is preferentially replaced by sulfur in any given case. If sufficient sulfur is introduced in the form of  $\text{H}_2\text{S}$  during the cyclization, the yield of **225** can be raised to 95%.<sup>7, 14a</sup>

c. *From Oxoalkyl Dithiocarboxylates.* The oxoalkyl dithiocarboxyl-



- a:  $\text{R}_1 = \text{C}_6\text{H}_5$ ;  $\text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{CH}_3$   
b:  $\text{R}_1 = \text{C}_6\text{H}_5$ ;  $\text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{C}_6\text{H}_5$   
c:  $\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{C}_6\text{H}_5$   
d:  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{H}$ ;  $\text{R}_3 = \text{C}_6\text{H}_5$   
e:  $\text{R}_1 = \text{CH}_3$ ;  $\text{R}_2 = \text{R}_3 = \text{C}_6\text{H}_5$

ates (**223**) postulated above as intermediates can be cyclized to the salts (**225**), with loss of  $\text{H}_2\text{O}$ , in the presence of strong acids.<sup>146a</sup> The triphenyl derivative (**225c**), for example, is obtained in 60% yield. The result is again considerably improved by the presence of  $\text{H}_2\text{S}$ , and the combination  $\text{H}_2\text{S}/\text{BF}_3$  in ether has been found to be particularly effective.<sup>7</sup>

The function of the  $\text{H}_2\text{S}$  in these reactions may be to convert the oxo group in **223** into the thione group, so making cyclization to **227** more probable than to **226**. According to Bergold,<sup>146c</sup> the elimination of water from 4-hydroxydihydro-1,3-dithiolium salts (**226**) having no alkyl or aryl substituent in position 4 is impossible by ordinary methods. E. Campaigne *et al.*<sup>146d</sup> have recently shown that **223b** can be cyclized directly to **225b** in the absence of  $\text{H}_2\text{S}$ , by using 70% perchloric acid or concentrated sulfuric acid and working under experimental conditions slightly different from those used by Leaver and Robertson. Under the same conditions good to very good yields of 2-*N,N*-dialkylamino-1,3-dithiolium salts (**225**) ( $\text{R}_1$  = dialkylamino) are obtained from  $\beta$ -keto-*N,N*-dialkyldithiocarbamates, and "4-aryl-isotrithionium salts" (**225**) ( $\text{R}_1$  = methylmercapto) can also be prepared by this method via the arylacyl trithiocarbonates<sup>146e</sup> (Sections III, B, 3 and III, B, 4).

d. *From Cyanoalkyl Dithiocarboxylates.* A fundamentally similar course is followed by the recently described preparation of 4-amino-1,3-dithiolium salts (**229**) from the cyanoalkyl dithiocarboxylates (**228**).<sup>147</sup> *N*-Alkyl (**230**) and *N*-acyl (**231**) derivatives of 4-amino-1,3-dithiolium salts are obtained when the acid-catalyzed cyclization is carried out in the presence of alkyl or acyl chlorides. The action of weak bases on the *N*-acyl derivatives leads to the stable betaines (**232**).

<sup>146a</sup> The condensation of the dithioacids with  $\alpha$ -halogen ketones does not always produce  $\beta$ -keto dithioesters (**223**). Somewhat surprisingly in several instances the reaction under mild alkaline conditions resulted in spontaneous ring closure to form the 4-hydroxy-1,3-dithiolan-2-ylidene derivatives, which in general under acidic treatment yield 1,3-dithiol-2-ylidene derivatives (Section III, A, 2, c).<sup>146b</sup>

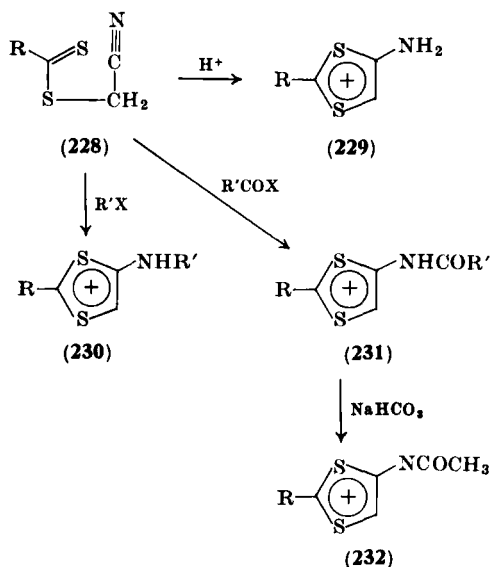
<sup>146b</sup> E. Campaigne and F. Haaf, *J. Heterocyclic. Chem.* **1**, 163 (1964).

<sup>146c</sup> W. Bergold, Dissertation, Freiburg-im-Breisgau (1961).

<sup>146d</sup> E. Campaigne, R. D. Hamilton, and N. W. Jacobsen, *J. Org. Chem.* **29**, 1708 (1964).

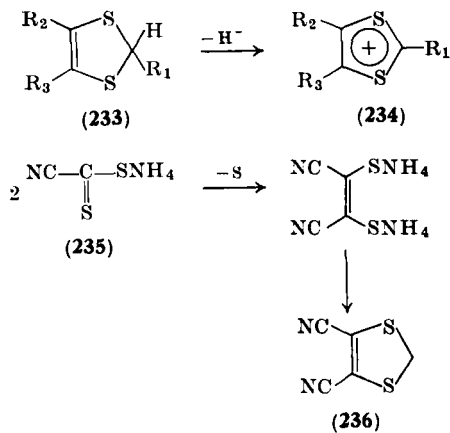
<sup>146e</sup> E. Campaigne and N. W. Jacobsen, *J. Org. Chem.* **29**, 1703 (1964).

<sup>147</sup> M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Japan* **36**, 1437 (1963).



## 2. From 1,3-Dithiole Derivatives

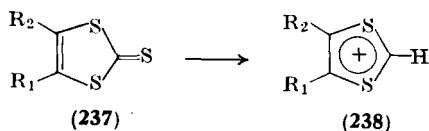
a. *Oxidation.* The preparation of 1,3-dithiolium salts by hydride abstraction from 1,3-dithiole and its derivatives (**233**) was in many cases implied in the one-step synthesis from benzene-1,2-dithiol and carbonyl compounds (Section III, A, 1, a). As was pointed out earlier, the tendency for the cations (**234**) to be formed depends very strongly



on the nature of the substituents. Thus the elimination of the hydride ion is naturally favored by electron-releasing substituents in position 2, and derivatives containing such substituents in this position are accordingly very sensitive towards oxidation.

Triphenyl-1,3-dithiole (**233**) ( $R_1 = R_2 = R_3 = C_6H_5$ ) has been converted into the corresponding salt by means of trityl perchlorate.<sup>24</sup> On the other hand, the 4,5-dicyano derivative (**236**) [which was first prepared by Bähr *et al.*<sup>148</sup> from carbon disulfide and ammonium cyanide by spontaneous desulfurization of the salts of cyanodithioformic acid (**235**), followed by ring closure with diiodomethane] is stable towards various oxidizing agents. The ease of oxidation of **233** to **234** is probably dependent on the same structural factors which govern the preparation of "dioxolenium salts" from 1,3-dioxolanes.<sup>149</sup>

b. *Reduction.* The Klingsberg process which is so useful for the preparation of 1,2-dithiolium salts from "trithiones" (Section II, A, 2, b) has also proved to be an excellent method for the direct conversion of "isotrithiones" (**237**) into simple 1,3-dithiolium salts (**238**); good results are obtained with peracetic acid in acetone<sup>150a</sup> and with hydrogen peroxide in glacial acetic acid.<sup>7</sup> This is in fact the only method by which the unsubstituted parent compound has been prepared.<sup>7</sup>



Wider use of this method for the preparation of dithiolium salts without fused-ring systems has so far been prevented by difficulties encountered in the preparation of "isotrithiones." However, the recently developed (but in some cases very laborious) syntheses of "isotrithiones" outlined in Scheme 10 open up many new possibilities.

c. *Exchange of Substituents.* In continuation of the principle of classification explained in Section II, A, 2, c, the present section

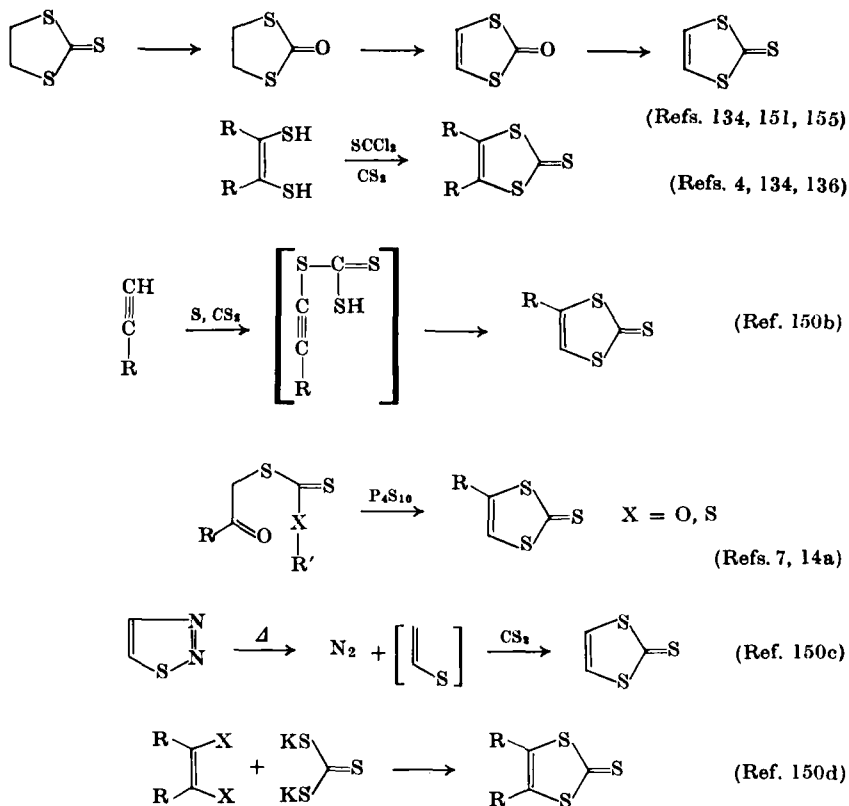
<sup>148</sup> G. Bähr, G. Schleitzer, and H. Bieling, *Chem. Tech. (Berlin)* **8**, 597 (1956); H. E. Simmons, R. D. Vest, and D. C. Blomstrom, *J. Am. Chem. Soc.* **84**, 4756, 4772, 4782 (1962).

<sup>149</sup> H. Meerwein, *Angew. Chem.* **67**, 374 (1955).

<sup>150a</sup> E. Klingsberg, *J. Am. Chem. Soc.* **84**, 3410 (1962); **86**, 5290 (1964); U.S. Patent 3,155,682 (1964); see *Chem. Abstr.* **62**, 6605 (1965).



includes formal syntheses of 1,3-dithiolium salts based on an electrophilic attack on the exocyclic group in **239**, or possibly in a vinylogous



SCHEME 10

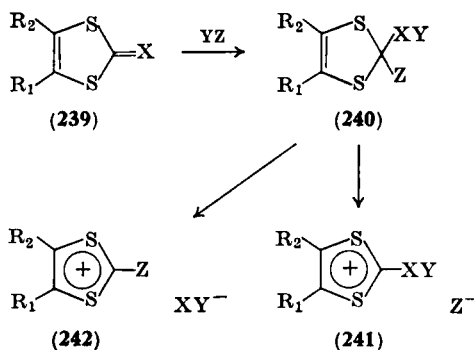
position, as in **246**, for example. Whether the initial product (**240**) loses Z to form **241** or loses XY to form **242** depends on the nature of the substituents.

<sup>150b</sup> R. Mayer, B. Gebhardt, J. Fabian, and A. K. Müller, *Angew. Chem.* **76**, 143 (1964).

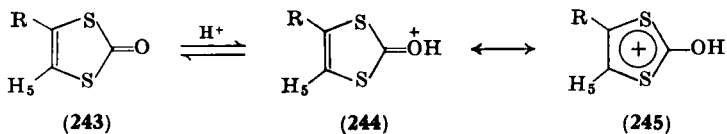
<sup>150c</sup> R. Huisgen and V. Weberndörfer, *Experientia* **17**, 566 (1961).

<sup>150d</sup> F. Runge, Z. El-Hewehi, H. J. Renner, and E. Taeger, *J. Prakt. Chem.* **11**, 284 (1960).

<sup>151</sup> H. Berger, Diplomarbeit, Freiburg-im-Breisgau (1963).



"Isodithione" (243) ( $\text{R} = \text{H}$ ) and its 4-aryl derivatives dissolve in trifluoroacetic acid or concentrated sulfuric acid without decomposition<sup>151</sup>; the basic strength of these compounds, however, and hence the equilibrium constant between 243 and 244, are unknown in either solvent. The fact that the electronic spectra in carbon disulfide and trifluoroacetic acid are very similar as regards the number, positions, and intensities of the maxima has been tentatively taken as an indication that the "isodithiones," unlike the isomeric "Baumann-Fromm disulfides," are, if at all, protonated only to a small extent in this acid.<sup>151</sup> It should, however, be recalled that in the case of  $\gamma$ -pyrone, for example, or even  $\gamma$ -pyridone, the electronic spectra of the cation and of the neutral molecule are very similar.<sup>152</sup> Thus, although the slight paramagnetic shift of the H-5 signal in the NMR spectra of the 4-aryl derivatives (243) (Section III, C, 4) on changing from carbon disulfide to trifluoroacetic acid is incompatible with a protonated species such as the 1,3-dithiolium limiting formula (245), i.e., with a strong electron deficiency in the ring, it does not rule out

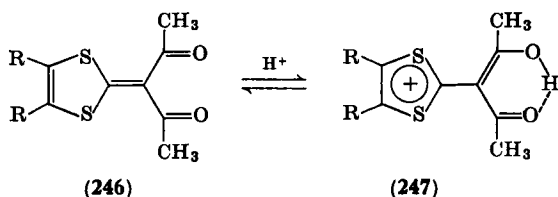


the existence of the conjugate acid, which is better represented in any case by the oxonium limiting formula (244).

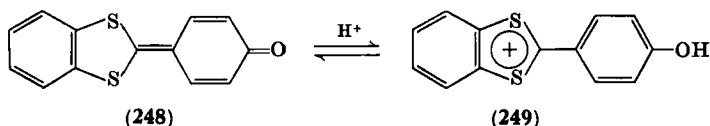
A detailed NMR study indicates that the conjugate acid (247) of

<sup>152</sup> A. Albert, in "Chemie der Heterocyclen", p. 272. Verlag Chemie, Weinheim, 1962.

the vinylogous "isodithione" (**246**) is stabilized by hydrogen bonding.<sup>153a,b,c</sup>



Basic properties are also shown by doubly vinylogous "isodithiones" of the type **248**, which are obtained by the action of bases on their conjugate acids.<sup>130</sup>



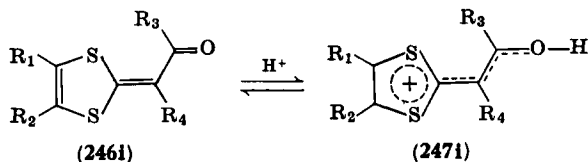
No alkoxy-1,3-dithiolium salts (**250**) are formed by the action of alkyl halides, dimethyl sulfate, or trialkyloxonium fluoroborates on "isodithiones," which, like the "Baumann-Fromm disulfides" (Section II, A, 2,c), are stable towards these reagents.<sup>134, 151, 154</sup>

The reactivity of "isotrithiones" towards alkylating agents has, however, been repeatedly confirmed. Both the parent compound and the 4-substituted derivatives react smoothly with alkyl halides or dimethyl sulfate to give very high yields of the preparatively very valuable 2-alkylmercapto-1,3-dithiolium ("isotrithionium") salts (**251**).<sup>134, 136, 138, 151, 153d, 155, 156a</sup>

<sup>153a</sup> E. Campaigne and R. D. Hamilton, *Abstr. Papers 147th Meeting, Philadelphia, Am. Chem. Soc.* p. 28N (1964).

<sup>153b</sup> E. Campaigne and R. D. Hamilton, *J. Org. Chem.* **29**, 1711 (1964).

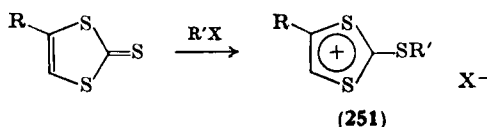
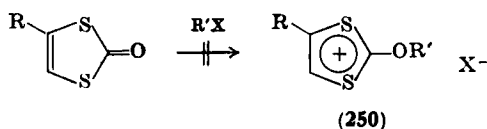
<sup>153c</sup> Some of the recently synthesized 1,3-dithiol-2-ylidene compounds of the type **246i** are strongly basic towards perchloric acid and yield the perchlorates (**247i**). However, on attempted recrystallization from ethanol these acids (**247i**) revert to the neutral compounds.<sup>153d</sup>



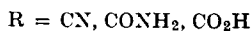
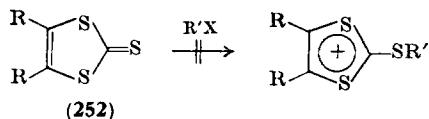
<sup>153d</sup> E. Campaigne and F. Haaf, *J. Org. Chem.* **30**, 732 (1965).

<sup>154</sup> H. Berger, Dissertation, Freiburg-im-Breisgau (1965).

<sup>155</sup> H. Baron, Dissertation, Freiburg-im-Breisgau (1956).



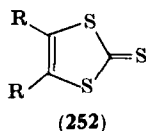
In "isotrithiones" of the type **252**, the —M and —I effects of the substituents in positions 4 and 5 oppose the formation of a positive charge in the ring, and alkylation of these compounds is consequently impossible.<sup>134, 150a</sup> This corresponds to the failure of the similarly substituted 1,3-dithioles (**236**) to undergo oxidation to the 1,3-dithiolium salts.



Very few data are at present available regarding the basic strength of the "isotrithiones." Like the "isodithiones" (**243**), they are soluble and stable in strong acids. From the close resemblance of the electronic spectra and of the H-5 shifts in the NMR spectra of the 4-aryl derivatives (**253**) in carbon disulfide and in trifluoroacetic acid, it is tentatively concluded that the neutral molecule predominates in the equilibrium between **253** and **254**.<sup>151, 156b</sup>

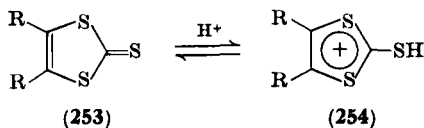
<sup>156a</sup> F. Challenger, A. E. Mason, E. C. Holdsworth, and R. Emmott, *J. Chem. Soc.* p. 292 (1953).

<sup>156b</sup> The base strength of a few "isotrithiones" has been studied in aqueous sulfuric acid at 25° by R. Mayer *et al.* using Hammett's indicator method (work to be published). As shown by the considerably higher  $H_0$  values the "isotrithiones" are weaker bases than the similarly substituted "trithiones."

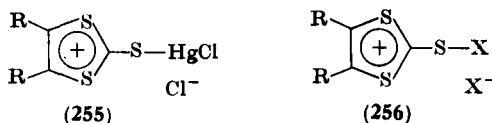


R	R	— $H_0$
H	H	5.24
—(CH <sub>2</sub> ) <sub>3</sub> —		4.93
—(CH <sub>2</sub> ) <sub>4</sub> —		4.75
—C <sub>4</sub> H <sub>4</sub> —		5.84

The many adducts of the "isotrithiones" with salts of heavy metals (e.g.,  $\text{HgCl}_2$ ) (255)<sup>7, 156a</sup> (which are valuable for the separation and

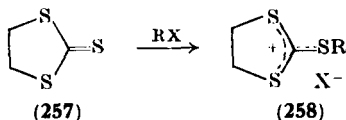


purification of these compounds) as well as the halogen ( $\text{Cl}_2$ ,  $\text{Br}_2$ ,  $\text{I}_2$ ) adducts (256)<sup>134, 156a</sup> (which are very sensitive to hydrolysis, although they can be isolated in the pure form) can also be formulated (at least formally) as 1,3-dithiolium salts.



No investigations on the saltlike nature of these adducts have as yet been reported. It is probably significant in this connection that similarly substituted "isodithiones" do not form adducts with these reagents, whereas simple thioketones can take part in corresponding additions.

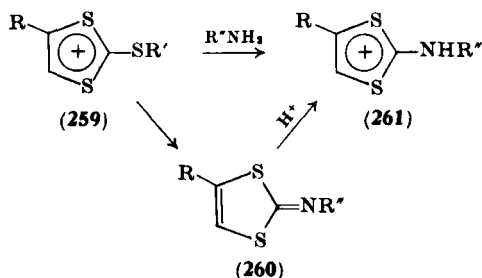
It should be mentioned at this point that the ease of alkylation of the "isotrithiones" to "isotrithonium salts" (251) is not due to any specific stability of the "2-methylmercapto-1,3-dithiolium ion," in which the  $\text{C}=\text{C}$  double bond takes part in the mesomeric system and contributes a pair of  $\pi$  electrons to the "aromatic sextet." As was recently shown by Wizinger *et al.*,<sup>138</sup> Gompper,<sup>157</sup> and Mayer and Schäfer<sup>158</sup> the "dihydroisotrithiones" (257) can also be readily alkylated by heating with alkyl halides, dimethyl sulfate, or ethyl *p*-toluenesulfonate. Results obtained so far indicate that the reactivity of these "dihydroisotrithonium salts" towards C, O, N, and S bases corresponds closely to that of the "isotrithonium salts."



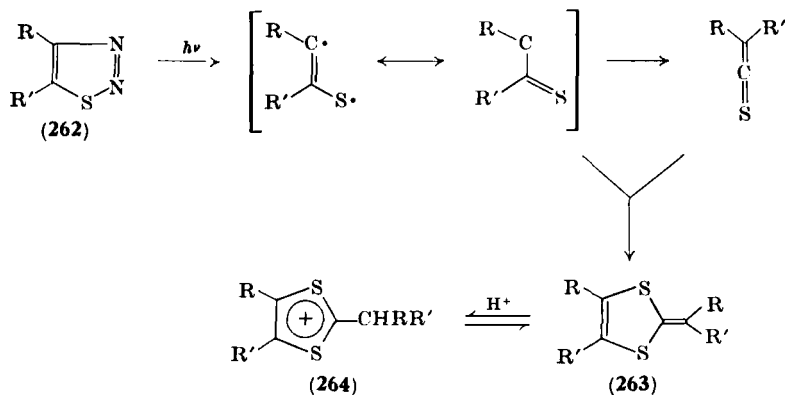
<sup>157</sup> R. Gompper and E. Kutter, *Angew. Chem.* **75**, 919 (1963).

<sup>158</sup> R. Mayer and K. Schäfer, *J. Prakt. Chem.* **26**, 279 (1964).

The reaction of the "isotrithionium iodide" (259) with aniline or phenylhydrazine to form the protonated anils or hydrazones (261) may actually involve the protonation of intermediate anils or hydrazones (260); the "isotrithione" itself, moreover, cannot be condensed with these bases.



Addor's synthesis of the hydrochlorides of the "benzoisotrithione imines" from benzene-1,2-dithiol and cyanogen chloride has already been discussed in detail (Section III, A, 1, a).



a:  $R = C_6H_5$ ;  $R' = H$

b:  $R = C_6H_5$ ;  $R' = CO_2R$

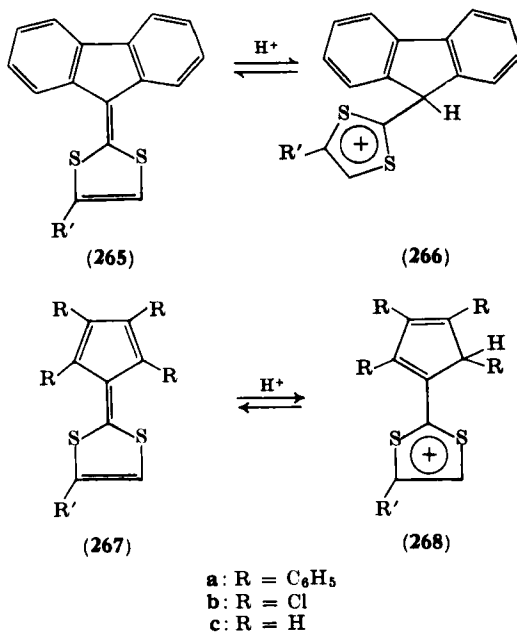
c:  $R = R' = C_6H_5$

The first definitely identified 1,3-dithiolium salts (264) without fused-ring systems were prepared by Kirmse and Horner by protonation of the 1,4-dithiafulvenes (263) obtained by the photolysis of aryl-substituted 1,2,3-thiadiazoles (262).<sup>159</sup>

<sup>159</sup> W. Kirmse and L. Horner, *Ann.* **614**, 4 (1958).

Like the iso- $\pi$ -electronic heptafulvenes,<sup>71</sup> the isomeric 1,2-dithiafulvenes (**52**), or the pyridonemethides,<sup>92</sup> the compounds of type **263** are typical anhydro bases. This relationship also extends to the 6,6-dicyano derivatives, which, like 8,8-dicyanoheptafulvene<sup>73</sup> and 6,6-dicyano-1,2-dithiafulvene (**52**), are not perceptibly protonated in anhydrous trifluoroacetic acid.

Many 3-alkyl- (**266**) and 3-alkenyl- (**268**) 1,3-dithiolium salts have been obtained by the protonation of the 1,4-dithiafulvalenes (**265** and **267**), which are vinylogs of **263**, and which, being analogs of sesquifulvalene, are also strongly basic. The structure of the conjugate acids has been established on the basis of electronic absorption measurements (Section III, C, 3), and above all from NMR data (Section III, C, 4). According to these results, protonation of similarly substituted 1,2- and 1,4-dithiafulvalenes occurs in corresponding positions.



## B. CHEMICAL PROPERTIES

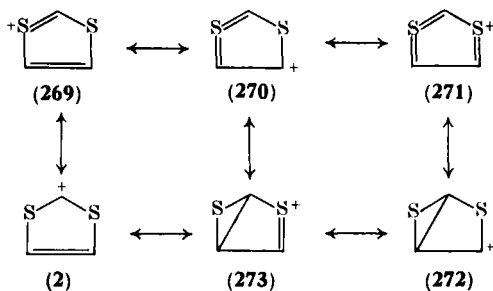
### 1. General Remarks

The fused-ring 1,3-dithiolium salts (**205**) are in some cases very sensitive to light, but are otherwise stable and easily manipulated.

Since this stability is evidently independent of the nature of the anions (which are readily interchangeable), the salts can be used together with more or less hydrophilic or lipophilic anions.

Most of the known salts without fused rings, on the other hand, are very unstable. Unfortunately, no quantitative studies have so far been carried out on the thermodynamic stability of the 1,3-dithiolium ion, and in view of the limited experimental data available it is impossible to draw any definite conclusions regarding the dependence of stability on the nature of the substituents. It is clear, however, that here the nature of the anion is of vital importance; thus whereas "4-(*p*-methoxyphenyl)-isotrithionium iodide" is stable, the phenyl derivative can be isolated only as the monomethyl sulfate.

The electrophilic character of the 1,3-dithiolium salts is distinctly stronger than that of the 1,2-dithiolium isomers. This has been very qualitatively explained by assuming that the positive charge is largely localized on the S—C—S grouping, i.e., that the most important of the limiting structures **2** and **269–273** are the carbonium–sulfonium structures **2** and **269**.

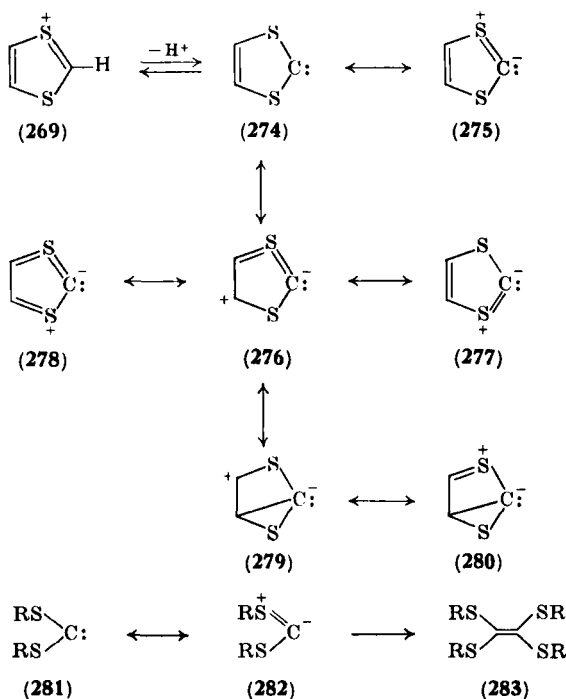


We have already seen that the one-electron deficit in the corresponding carbonium-sulfonium structures of the 1,2-dithiolium ion (**1**) (Section II, B, 1) is distributed over two equivalent carbonium structures. The electrophilic character of these two equivalent C-3 and C-5 positions should therefore be weaker than that of C-2 in **2**, in spite of the fact that C-2 is flanked by two sulfur atoms which tend to reduce the charge.

The 1,3-dithiolium ion is the conjugate acid of the dithiocarbene (**274**). Bisalkylmercaptocarbenes (**281**) have recently been postulated by several research groups as discrete intermediates in the formation of the tetrakis-alkylmercaptoethylenes (**283**) from *o*-thioformates and



strong bases<sup>160, 161</sup> and in the thermal decomposition of the toluene-sulfonylhydrazone salts of trithiocarbonates.<sup>162, 163</sup> The fact that such thiocarbenes could be intercepted only with the aid of very strong nucleophiles indicates the weak electrophilic character of these compounds and the existence of efficient internal stabilization in the sense shown by **282**.<sup>163</sup>



This resonance stabilization should be even more pronounced in the cyclic dithiocarbene (**274**), as indicated by the neutral carbene structure (**274**) and the ylid structures (**275–280**), in which the potential “aromatic sextet” of the 1,3-dithiolium ion is retained. Consequently, H-2 in **269** should be acidic. The analogy with the thiazolium and imidazolium ions, which have been intensively studied by Bres-

<sup>160</sup> J. Hine, R. P. Bayer, and G. G. Hammer, *J. Am. Chem. Soc.* **84**, 1751 (1962).

<sup>161</sup> A. Fröling and J. F. Arens, *Rec. Trav. Chim.* **81**, 1009 (1962).

<sup>162</sup> U. Schöllkopf and E. Wiskott, *Angew. Chem.* **75**, 725 (1963).

<sup>163</sup> D. M. Lemal and E. H. Banitt, *Tetrahedron Letters* **5**, 245 (1964).

low<sup>164</sup> and Wanzlick<sup>165</sup> is obvious. The further fact that 1,3-dimethylimidazolium iodide, like 3,4-dimethylthiazolium bromide, undergoes rapid H-D exchange led Breslow to conclude that, in the thiazolium zwitterion, the sulfur probably stabilizes the anion only by an inductive effect, and that resonance, as in **276–278**, for example, plays no part.

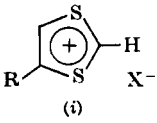
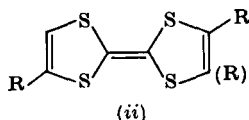
No reactions of **269** with correspondingly strong and sterically hindered bases and no H-D exchange experiments have so far been reported.<sup>165a</sup> In the paper published in 1926 by Hurtley and Smiles,<sup>131</sup> however, the authors described results that could be explained by deprotonation of the benzo-1,3-dithiolium ion (**284**) (which should be a weaker acid than **269**, owing to the fused aromatic ring) to the benzodithiocarbene (**285**).

When benzo-1,3-dithiolium tetrachlorozincate is heated in acetic anhydride, a 30% yield of dibenzotetrathiafulvalene (**286**) is obtained. Compound **286** is also formed, together with "benzoisodithione," during the pyrolysis of the spiro compound (**287**), and its structure has been confirmed by independent synthesis from 1,2-benzenedithiol and tetrachloroethylene.

<sup>164</sup> R. Breslow, *J. Am. Chem. Soc.* **80**, 3719 (1958).

<sup>165</sup> H. W. Wanzlick, *Angew. Chem.* **74**, 129 (1962); H. W. Wanzlick and H. J. Kleiner, *Ber.* **96**, 3024 (1963).

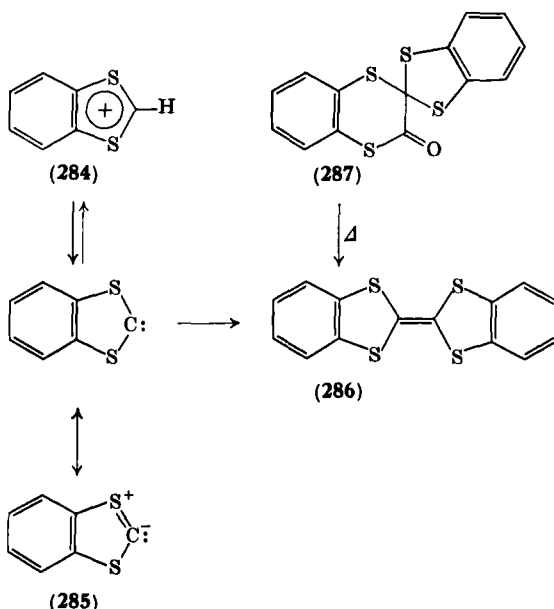
<sup>165a</sup> In the meantime the following half-lives of the hydrogen-deuterium exchange of the hydrogens in the 2-position of the 1,3-dithiolium salts (*i*) have been determined using NMR spectrometry [60% (v/v) CF<sub>3</sub>CO<sub>2</sub>D/D<sub>2</sub>O; 34°].

 (i)		
	R (X <sup>-</sup> )	t <sub>1/2</sub>
 (ii)	CH <sub>3</sub> (ClO <sub>4</sub> <sup>-</sup> )	166 ± 15 min
	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (p) (HSO <sub>4</sub> <sup>-</sup> )	36 ± 5 min
	C <sub>6</sub> H <sub>5</sub> (HSO <sub>4</sub> <sup>-</sup> )	34 ± 5 min

When the acids (*i*) are treated with an excess of *N*-ethyldiisopropylamine the 1,4,5,8-tetrathiafulvalenes (*ii*) are formed as mixtures of the geometrical isomers.<sup>165b</sup>

<sup>165b</sup> H. Prinzbach, H. Berger and A. Lüttringhaus, *Angew. Chem.* **77**, 453 (1965).

The formation of **286** from **285** could also be compared with the dimerization of dimethoxycarbenes to tetramethoxyethylenes.<sup>166-168</sup>



## 2. Reactions with Nucleophilic Reagents

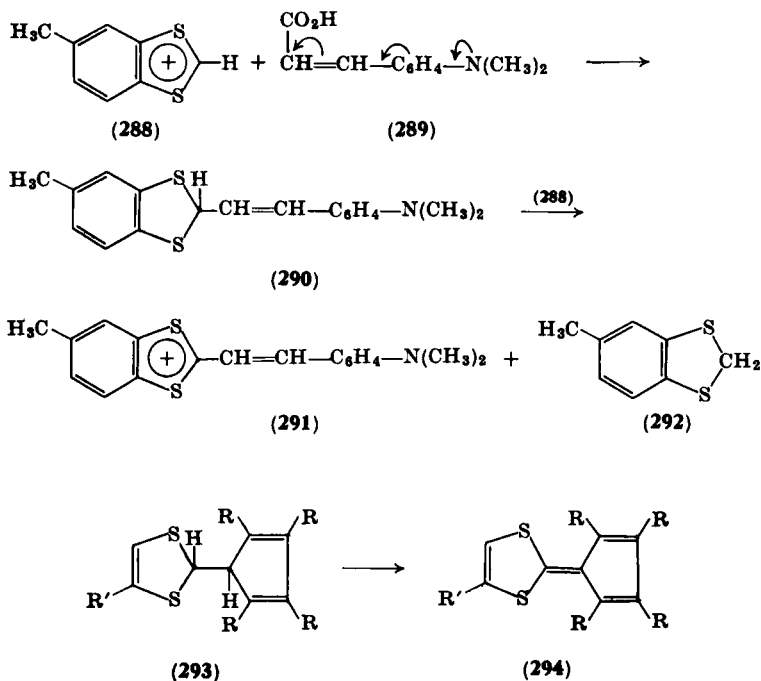
The ability of the 1,3-dithiolium system to act as a hydride acceptor was first studied in detail in connection with the formation of the color salt (**291**).<sup>4</sup> If equimolar quantities of **288** and **289** are used, the yield after a short reaction time is about 50%; when 2 moles of **288** are used, on the other hand, the yield is almost quantitative. This agrees with the reaction sequence given above, although no efforts were made to isolate and characterize the 1,3-dithiole (**292**).

The 1,3-dithiolium salt also acts as an oxidizing agent in the reaction with the sodium salt of tetraphenylcyclopentadiene in the absence of air. Besides the dihydro-1,4-dithiafulvalene (**293**), the products of this reaction include varying quantities of the 1,4-dithiafulvalene (**294**).<sup>154</sup>

<sup>166</sup> R. W. Hoffmann and H. Häuser, *Angew. Chem.* **76**, 587 (1964).

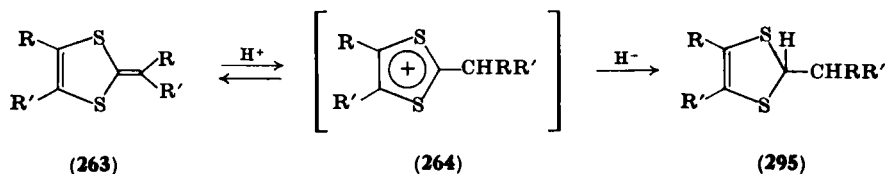
<sup>167</sup> D. M. Lemal, E. P. Gosselink, and A. Ault, *Tetrahedron Letters* **11**, 579 (1964).

<sup>168</sup> U. Schmidt and K. H. Kabitzke, *Angew. Chem.* **76**, 687 (1964).



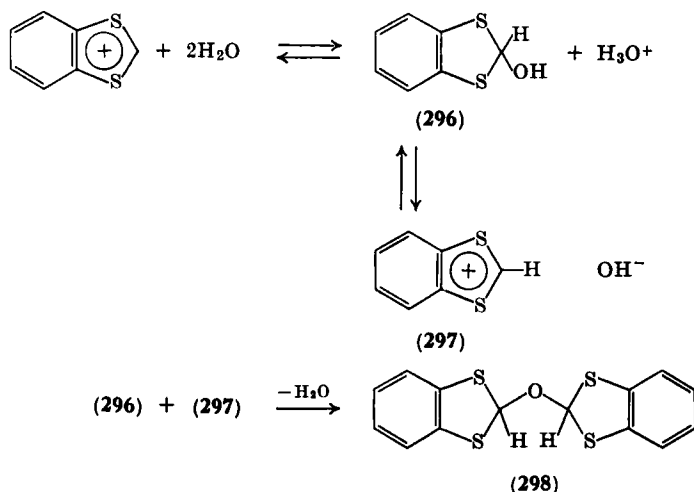
The exocyclic C=C double bond of the 1,4-dithiafulvenes (**263**) can be selectively hydrogenated under controlled conditions in an acidic medium (Zn/glacial acetic acid), the product being **295**. The ease with which the postulated intermediate 1,3-dithiolium salts (**264**) accept the hydride ion has been adduced as evidence that the resonance stabilization of these ions cannot be very strong.<sup>159</sup>

The course of the reduction in strong mineral acids is very complex.

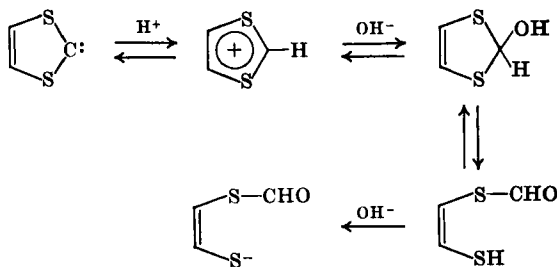


The benzo-1,3-dithiolium salts behave towards water as typical Lewis acids. The products probably exist essentially in the form of nonionized carbinols (**296**).<sup>4, 181</sup> As can be expected by analogy with

tropylalcohol<sup>169</sup> or many heterocyclic analogs,<sup>170</sup> the equilibrium  $(296) \rightleftharpoons (297)$  leads to the formation of the dimolecular ether  $(298)$ . The formation of the alcohol and that of the ether are reversed on the addition of acid.



We saw in the last section that at least the more strongly acidic nonfused 1,3-dithiolium ion can also act as a Brönsted acid; the ring-chain equilibrium, however, indicated in Scheme 11 is in absence of convincing experimental data at present largely speculative.



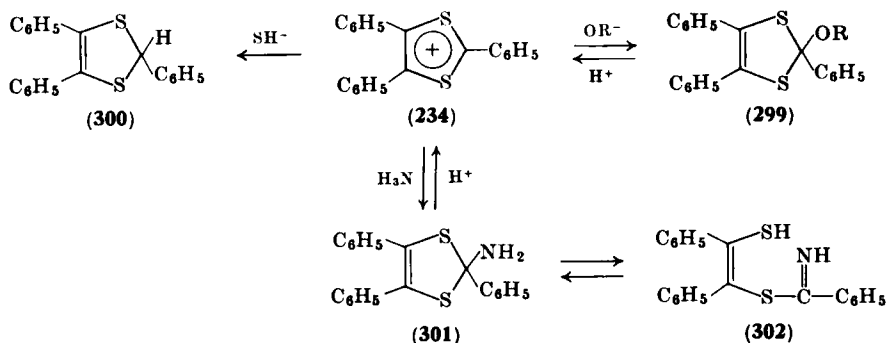
SCHEME 11

The addition product  $(299)$  corresponding to the carbinol  $(296)$  has been isolated in the pure form by the action of the ethoxide ion on the

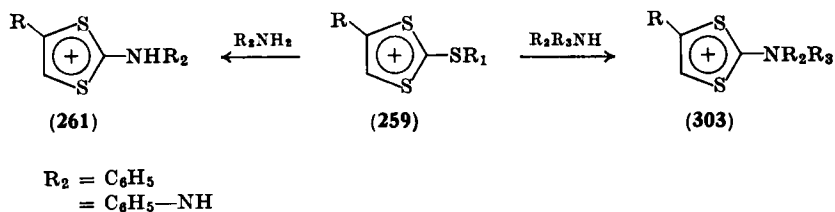
<sup>169</sup> W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **76**, 3203 (1954).

<sup>170</sup> D. Beke, *Advan. Heterocyclic Chem.* **1**, 167 (1963).

2,4,5-triphenyl salt (**234**). Compound **299** is quantitatively reconverted into **234** by treatment with perchloric acid. Reduction of **234** by boiling for a short time with NaSH in ethanol yields the dithiole (**300**); the details of this reaction are not yet certain. The dithiole (**300**) can be reoxidized to **234** by trityl salts.



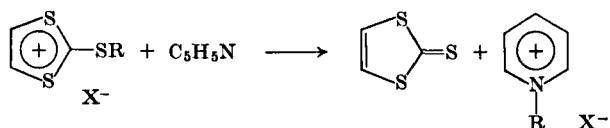
The aminodithiole (**301**) obtained from **234** and ammonia in benzene solution can also be isolated at room temperature. It can again be completely reconverted into **234** by means of perchloric acid. Compound **301** decomposes in boiling ethanol, with liberation of hydrogen sulfide; in addition to a little elementary sulfur, a little desoxybenzoin, thiobenzamide, and triphenyl 1,3-thiazole, the dithiole (**300**) was isolated in 20% yield. Leaver has explained this result on the basis of the equilibrium between **301** and **302** and the exchange of the amino group for the sulfhydryl group.<sup>24</sup>



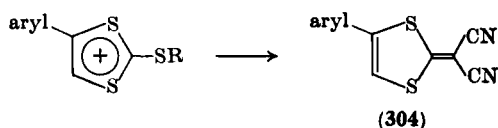
Just as primary aromatic amines replace the  $\text{CH}_3\text{S}$  group of the "isotriphenyl salts" (**259**) to form protonated anils or hydrazones (**261**), the reaction with aliphatic amines such as piperidine or morpholine leads to **303**.

The action of the tertiary amine pyridine, on the other hand, has

been observed<sup>134, 171</sup> to lead to transmethylation, i.e., nucleophilic attack on the alkylmercapto group instead of at position 2.

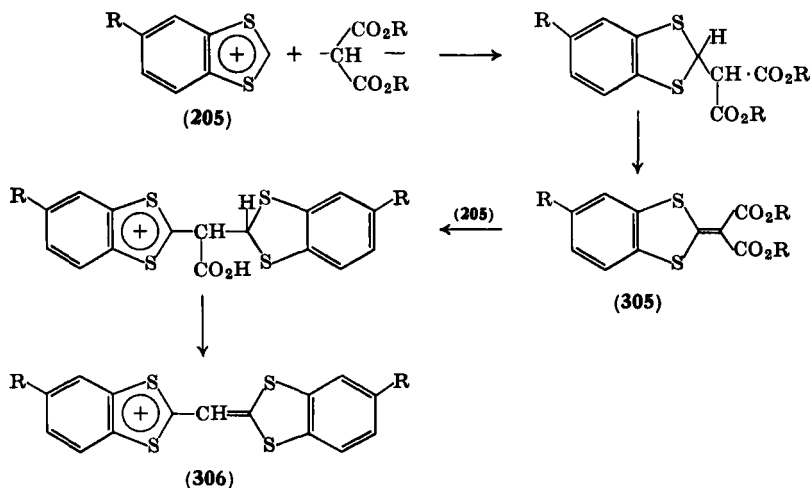


Compound **259** (R = aryl) also reacts with malonic dinitrile, without the addition of special bases, to form the 1,4-dithiafulvene (**304**).<sup>151</sup> Campaigne *et al.*<sup>153a, b, d</sup> successfully carried out similar condensations in boiling glacial acetic acid/pyridine.<sup>172</sup>



The behavior of the fused-ring benzo-1,3-dithiolium salts towards strong C—H acids has been described in particular by Wizinger *et al.*<sup>132, 136, 138, 139</sup>

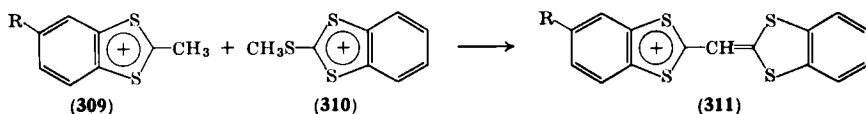
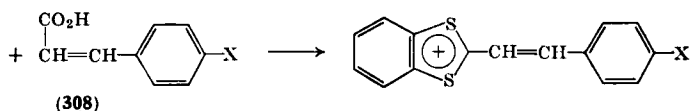
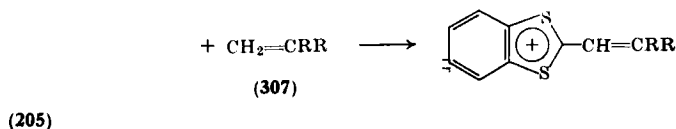
The reaction of **205** with malonic ester leads, by double decarboxylation and dehydrogenation, to the formation of the monomethine color salt (**306**).



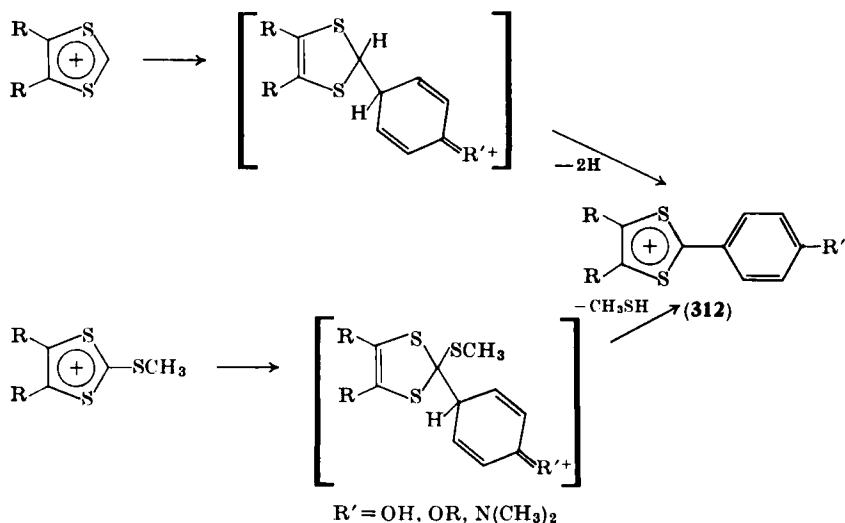
<sup>171</sup> E. Campaigne, T. Bosin, and R. D. Hamilton, *J. Org. Chem.* **30**, 1677 (1965).

<sup>172</sup> H. Behringer and R. Wiedenmann, *Tetrahedron Letters* **41**, 3705 (1965).

The attack of the anion **205** on **305** finds parallels in many reactions of 1,3-dithiolium salts with 1,1-disubstituted olefins such as **307** and



with cinnamic acid derivatives such as **308**,<sup>136, 138</sup> as well as in the reactions with many conjugate acids of relatively strongly basic olefins, as exemplified by the condensation of **309** with **310** to form the monomethine salt **(311)**.<sup>136</sup>



Slight differences in the electrophilic character of 1,2- and 1,3-dithiolium salts are shown by their behavior towards aromatic compounds. As in the 1,2-dithia series, dimethylaniline undergoes



electrophilic substitution in position 4 both by the 1,3-dithiolium salts and by their 2-methylmercapto derivatives.<sup>132, 150a</sup> However, whereas "trithonium salts" cannot generally substitute phenols or phenol ethers (no results have so far been reported for 1,2-dithiolium salts with no substituents in positions 3 or 5), the 1,3-dithiolium salts and the "isotrithonium salts" are sufficiently electrophilic to attack these relatively weakly activated aromatic compounds, to form **312**.<sup>132</sup> Azulene too is substituted in 1-position by the "benzoisotrithonium" perchlorate.<sup>173a</sup>

It should again be pointed out at this stage that the reactivity of the "dihydroisotrithonium salts" in pyridine/triethylamine or glacial acetic acid/pyridine towards active methylene compounds and towards phenols is comparable to that of the "isotrithonium salts."<sup>157, 158</sup>

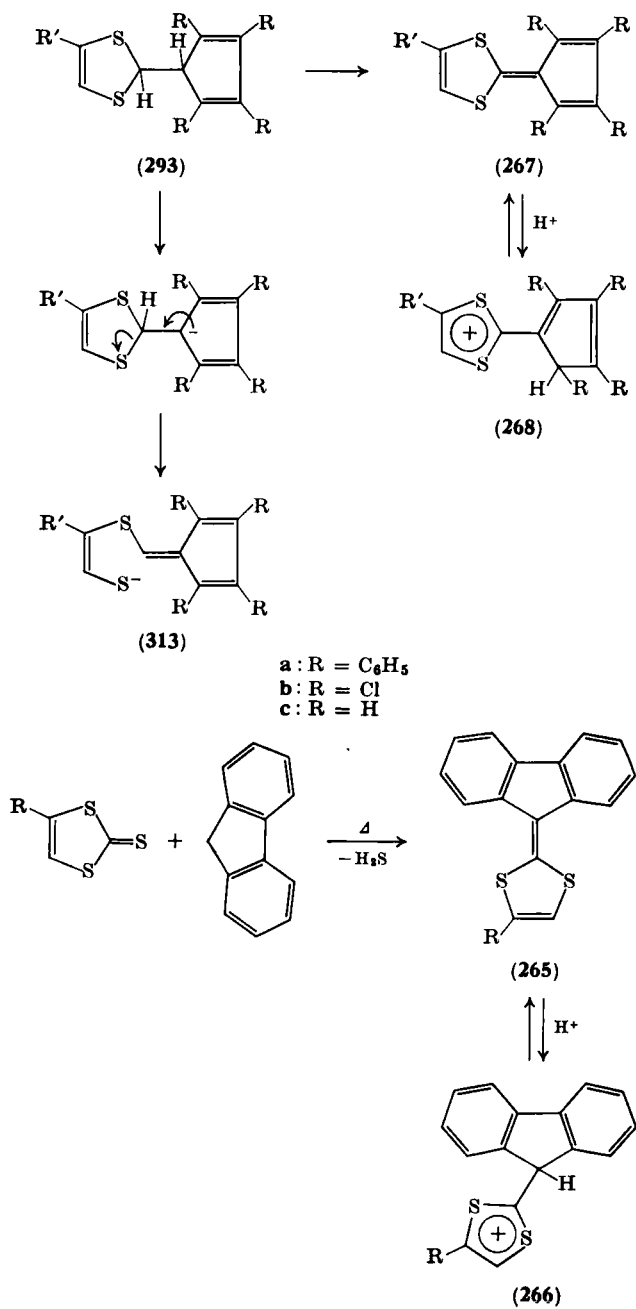
Weak C—H acids such as cyclopentadiene, indene, or fluorene are not alkylated either by 1,3-dithiolium salts or by "isotrithonium salts" without the help of a very strong base.<sup>154, 157</sup> 4-Aryl-1,3-dithiolium salts react with the sodium salts of tetraphenylcyclopentadiene or fluorene to give a 10–20% yield of the 1,4-dithiafulvalenes **265** or **267a** the intermediates (**293**) are rapidly oxidized by the dithiolium salt. The metalation of **293** by the cyclopentadienyl sodium, on the other hand, probably causes ring opening to form **313** and is therefore responsible for the large number of by-products obtained. This side reaction is analogous to the well-known cleavage of 1,3-dithiolane-2-thiones by nucleophilic reagents.<sup>158</sup> These competing reactions become predominant when cyclopentadienyl or indenyl sodium is used. On the other hand, the "isotrithonium salts" react with tetrachlorocyclopentadiene in absolute methanol and under N<sub>2</sub> to give a yield of more than 90% of **267b**, and with cyclopentadienyl sodium to give the unsubstituted 1,4-dithiafulvalene (**267c**, R' = H).<sup>173a, b</sup>

1,4-Dithiafulvalenes (**265**) of the doubly fused type, like their 1,2-dithia analogs (Section II, B, 2), are more easily obtained, although sometimes only in moderate yields, by the reaction of the thermally stable "4-arylisotrithiones" with fluorene in the fused state.<sup>154</sup>

These 1,4-dithiafulvalenes are comparable in their basic strength with the isomeric 1,2-dithiafulvalenes. They react with acids to form

<sup>173a</sup> R. Gompper and E. Kutter, *Ber.* **98**, 2825 (1965).

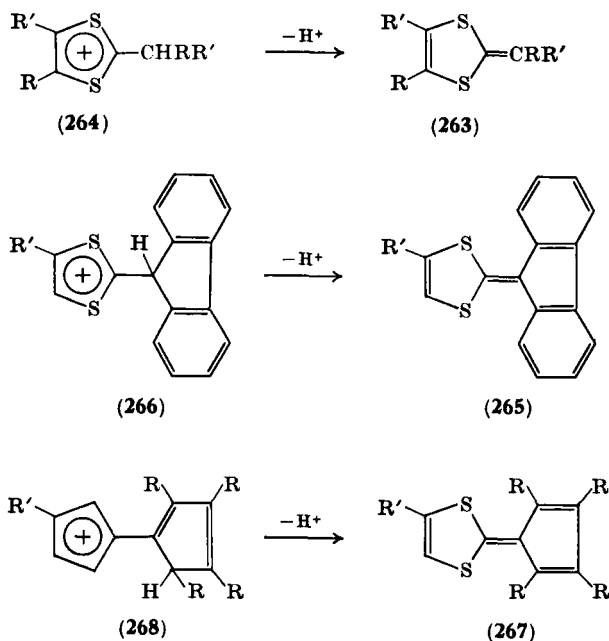
<sup>173b</sup> M. Brown, U.S. Patent 3,057,875 (Cl. 260–327) (1962); see *Chem. Abstr.* **58**, 6837 (1963).



a series of alkyl- (266) and alkenyl- (268) 1,3-dithiolium salts, the structures of which have again been established mainly on the basis of UV absorption data (Section III, C, 3) and NMR measurements (Section III, C, 4).

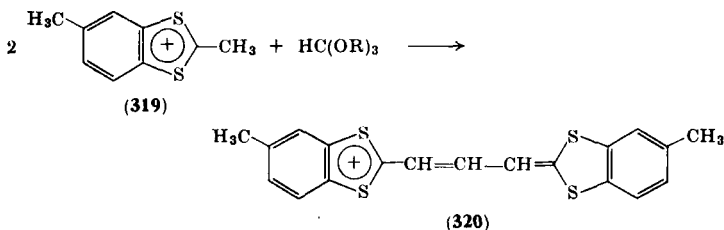
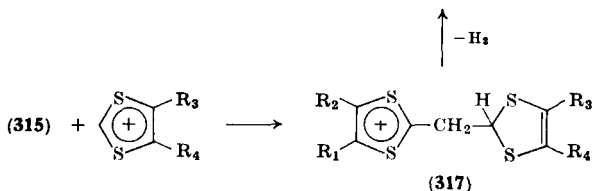
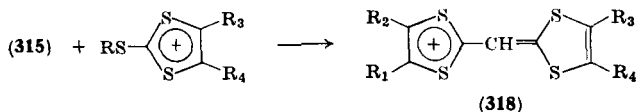
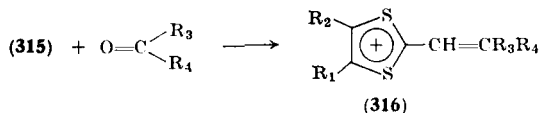
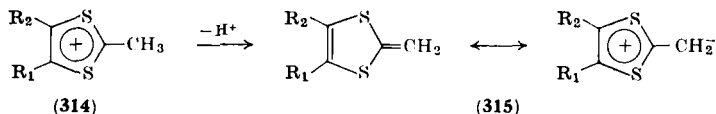
### 3. Side Chain Reactivity

The 2-substituted 1,3-dithiolium salts (264, 266, and 268) are already familiar as the conjugate acids of the 1,4-dithiafulvenes (263) and 1,4-dithiafulvalenes (265 and 267). Weak bases such as water or aqueous soda solution are sufficient to displace the equilibrium completely in favor of the neutral compounds.<sup>151, 154</sup>



“Isotrithionemethides” (315) probably also occur as intermediates in the condensation of 2-methyl-1,3-dithiolium salts (314) with various carbonyl compounds to form products (316). These salts

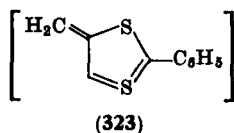
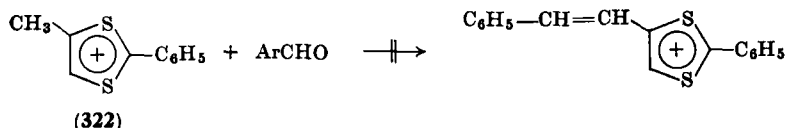
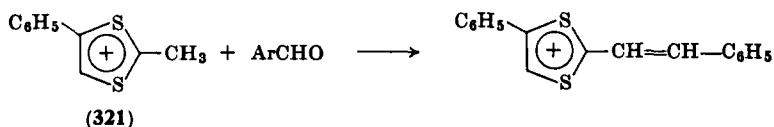
react with aldehydes in glacial acetic acid without the aid of special bases; the addition of strong bases becomes necessary only when the carbonyl component is a ketone or a pyrone.<sup>132, 136</sup>



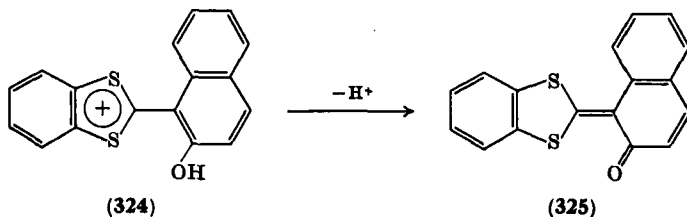
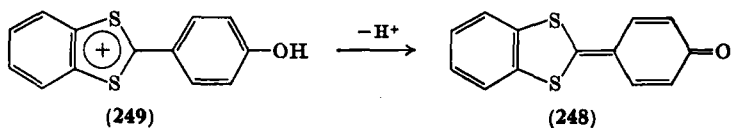
The 2-methyl-1,3-dithiolium salts (314), in the form of the readily polarizable anhydro bases (315), suffer electrophilic attack by both "isotrithionium salts" and 1,3-dithiolium salts, the product in each case being the monomethine salt (318). It is not known whether the intermediate (317) is oxidized by excess dithiolium salt or by atmospheric oxygen. Trimethine dyes such as 320 have been obtained by the reaction of orthoformates with the monomethide that exists in equilibrium with 319.

The high mobility of the 2-methyl protons in **314** is further confirmed by the ability of these compounds to couple with diazonium salts.<sup>132</sup>

The fact that the delocalization of the positive charge from position 2 into position 4 is only slight, as well as the unfavorable energy

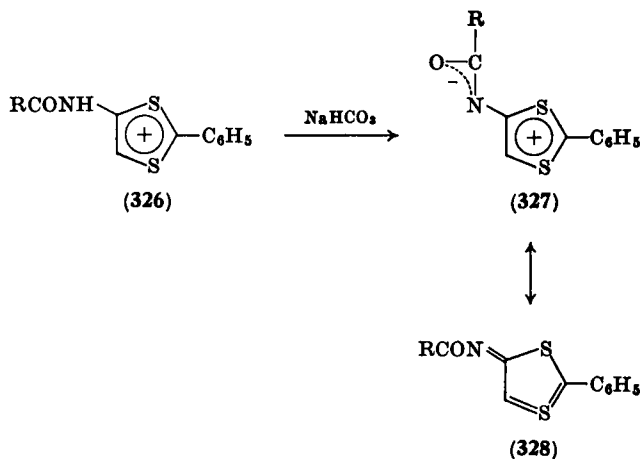


conditions in the anhydro base (323) (in which one of the ring sulfur atoms must assume the decet configuration), are particularly clear from the difference in the behavior of the salts **321** and **322**; thus whereas the methyl group in **321** condenses with benzaldehyde without the aid of additional base, the methyl group in **322** is resistant towards aromatic aldehydes, even in the presence of pyridine or triethylamine.



The weak basicity of the "isodithiones" is also apparent from the very high acidity of the vinylogous conjugate acids (**247**, **249**, and **324**).<sup>130, 153d</sup> Even in very weak bases, such as aqueous  $K_2CO_3$ , the equilibrium is displaced almost completely in favor of the anhydro bases (**246**, **248**, and **325**).

Whereas the hydrogen atoms of a methyl group in position 4 or 5 of the 1,3-dithiolium ion are inert towards strong bases, the amide proton in **326** can be split off by an aqueous solution of sodium bicarbonate.<sup>147</sup>



In the corresponding base, i.e., the betaine (**327**), charge neutralization is possible only in a limiting structure (**328**) in which one of the sulfur atoms possesses a deficit of electrons.

### C. PHYSICAL PROPERTIES

#### 1. Quantum Mechanical Calculations

Zahradnik and Koutecky<sup>1, 122</sup> have carried out quantum mechanical calculations for the 1,3-dithiolium ion, using the simple MO LCAO method together with the rather arbitrary experimental parameters used in the calculations for the 1,2-dithiolium ion (Section II, C, 1). The lowest relative electron density in both molecular diagrams (Fig. 5) is assigned to position 2; the C-4—C-5 bond order in both cases is very high, and approximates to the value for an isolated  $C=C$  double bond. The calculated delocalization energy of this ion,

i.e., 25 kcal/mole,<sup>174</sup> is appreciably lower than, e.g., the calculated value of 46 kcal/mole for the thiopyrylium ion.<sup>175</sup>

According to these diagrams of the ground state, nucleophilic

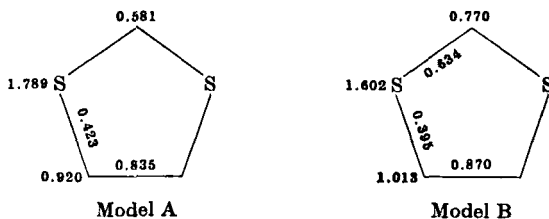


FIG. 5. Molecular diagrams of the 1,3-dithiolium cation (relative electron densities and bond orders).

reagents should attack exclusively in position 2, and the C-4—C-5 bond should exhibit typical dienophilic behavior. Whereas no exceptions to the former requirement have been observed, no reactions of **2** with dienes have so far been reported.

The benzo-1,3-dithiolium cation has also been subjected to the theoretical treatment, on the basis of model A, and using  $\beta_{CS}$  values of between 0.6 and 1.0. It was found that electrophilic substitution should occur most readily in position 4, whereas nucleophilic or free-radical attack should take place exclusively in position 2. The possibility of correlating the excitation energies as calculated by the HMO method with the values found by experiment has been studied, and the limitations of such a correlation discussed.<sup>1</sup>

Figures 6 and 7 show the molecular diagrams of "isotrithione" and "isodithione," respectively, based on the same models.<sup>122</sup>

As expected, the C-4—C-5 bond orders found for these derivatives of the 1,3-dithiolium system are even higher. Contrary to the theoretical expectations, however, Mayer and Gebhardt<sup>134</sup> have recently found that halogens do not add to these compounds, and both "isotrithione" and "isodithione" are stable towards butadiene or furan under conditions in which vinylene carbonate readily enters into Diels-Alder reactions;<sup>176</sup> under drastic conditions, "isodithione" gives an adduct with cyclopentadiene, but the structure of this adduct is not yet known.

<sup>174</sup> J. Koutecky, *Collection Czech. Chem. Commun.* **24**, 1608 (1959).

<sup>175</sup> J. Koutecky, J. Paldus, and R. Zahradnik, *Collection Czech. Chem. Commun.* **25**, 617 (1960).

<sup>176</sup> M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.* **77**, 3789 (1955).

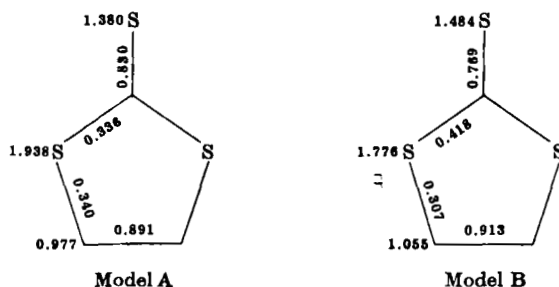


FIG. 6. Molecular diagrams of 1,3-dithiole-2-thione ("isotrithione") (relative electron densities and bond orders).

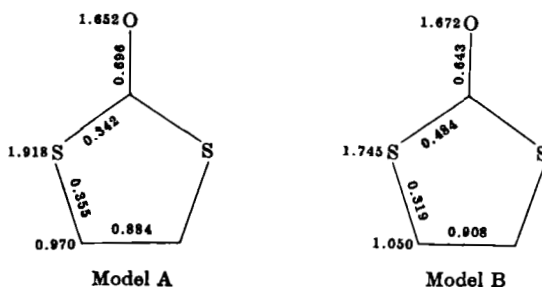


FIG. 7. Molecular diagrams of 1,3-dithiol-2-one ("isodithione") (relative electron densities and bond orders).

## 2. Molecular Structure

The dimensions of the unit cells of 2,4-diphenyl- and 2,4,5-triphenyl-dithiolium perchlorate and of the simple "isotrithione" have been determined (Section II, C, 2). Accurate molecular data, however, are lacking.<sup>126</sup>

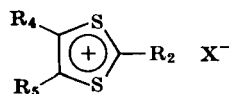
## 3. IR and Electronic Absorption Data

Only a few IR data for 1,3-dithiolium salts have so far been reported,<sup>151, 154</sup> and no systematic investigations have as yet been carried out on the "isotrithiones"<sup>153a</sup> and "isodithiones."

The currently available electronic absorption data for 1,3-dithiolium salts are summarized in Table XV. First attempts at a theoretical



TABLE XV  
ELECTRONIC ABSORPTION DATA OF 1,3-DITHIOLIUM SALTS



No.	R <sub>2</sub>	R <sub>4</sub>	R <sub>5</sub>	Solvent	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	Reference
1	H	H	H	C <sub>2</sub> H <sub>5</sub> OH/HClO <sub>4</sub>	212; 254	3,390; 3,000	<i>a</i>
2	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub> OH/HClO <sub>4</sub>	209; 269; 362	11,300; 3,720; 15,500	<i>a</i>
3	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	H	H	C <sub>2</sub> H <sub>5</sub> OH/HClO <sub>4</sub>	515		<i>b</i>
4	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>5</sub>	H	70% HClO <sub>4</sub>	243; 278; 390	15,500; 10,250 12,030	<i>c</i>
5	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>4</sub> —Br (4)	H	70% HClO <sub>4</sub>	253; 284; 395	17,400; 14,140; 12,900	<i>c</i>
6	C <sub>6</sub> H <sub>4</sub> —N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	70% HClO <sub>4</sub>	225; 262; 295; 375	12,900; 10,970; 13,500; 20,000	<i>c</i>
7	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	C <sub>2</sub> H <sub>5</sub> OH/HClO <sub>4</sub>	218; 242; 305; 392	14,500; 15,900 6,300; 15,900	<i>a</i>
8	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OH/HClO <sub>4</sub>	221; 303; 399	25,200; 95,500; 15,700	<i>a</i>
9	H	C <sub>6</sub> H <sub>5</sub>	H	CF <sub>3</sub> CO <sub>2</sub> H	347	2,250	<i>d</i>
10	H	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	CF <sub>3</sub> CO <sub>2</sub> H	286; 388	12,600; 2,600	<i>d</i>
11	(CH <sub>3</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	95% C <sub>2</sub> H <sub>5</sub> OH	245; 303	800; 3,100	<i>e</i>

12	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>5</sub>	H	70% HClO <sub>4</sub>	225; 235; 300; 315	16,200; 14,100; 10,700; 12,030	<i>e</i>
13	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>4</sub> —CH <sub>3</sub> (4)	H	95% C <sub>2</sub> H <sub>5</sub> OH	228; 242; 302; 320	13,800; 13,500; 10,700; 10,960	<i>e</i>
14	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>4</sub> —Cl (4)	H	95% C <sub>2</sub> H <sub>5</sub> OH	230; 237; 305; 315	17,000; 16,600; 14,450; 14,130	<i>e</i>
15	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	H	95% C <sub>2</sub> H <sub>5</sub> OH	256; 292; 326	12,600; 13,200; 10,250	<i>e</i>
16	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>4</sub> —OH (4)	H	95% C <sub>2</sub> H <sub>5</sub> OH	261; 292; 330	12,300; 12,900; 9,120	<i>e</i>
17	(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	95% C <sub>2</sub> H <sub>5</sub> OH	223; 255; 323	20,900; 9,120; 20,900	<i>e</i>
18	(CH <sub>3</sub> ) <sub>2</sub> N	OH	H	70% HClO <sub>4</sub>	242	15,500	<i>f</i>
19	CH <sub>3</sub> S	C <sub>6</sub> H <sub>5</sub>	H	70% HClO <sub>4</sub>	240; 282; 373	18,630; 7760; 13,800	<i>f</i>
20	CH <sub>3</sub> S	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	H	70% HClO <sub>4</sub>	232; 268; 315; 368	15,500; 9,550; 7,950; 22,900	<i>f</i>
21	CH <sub>3</sub> S	OH	H	70% HClO <sub>4</sub>	221; 305	1,950; 15,850	<i>f</i>
22	C <sub>6</sub> H <sub>5</sub>	OH	H	70% HClO <sub>4</sub>	244; 275; 367	3,230; 2,950; 15,150	<i>f</i>

<sup>a</sup> D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.* p. 5104 (1962).

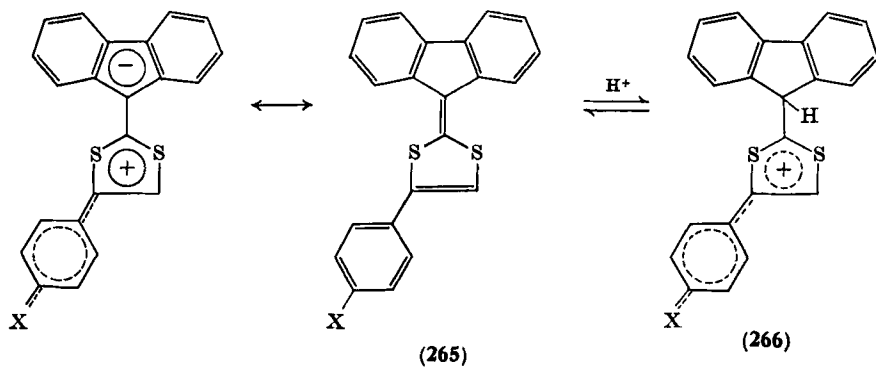
<sup>b</sup> E. Klingsberg, *J. Am. Chem. Soc.* **84**, 3410 (1962).

<sup>c</sup> E. Campaigne and R. D. Hamilton, *J. Org. Chem.* **29**, 1711 (1964).

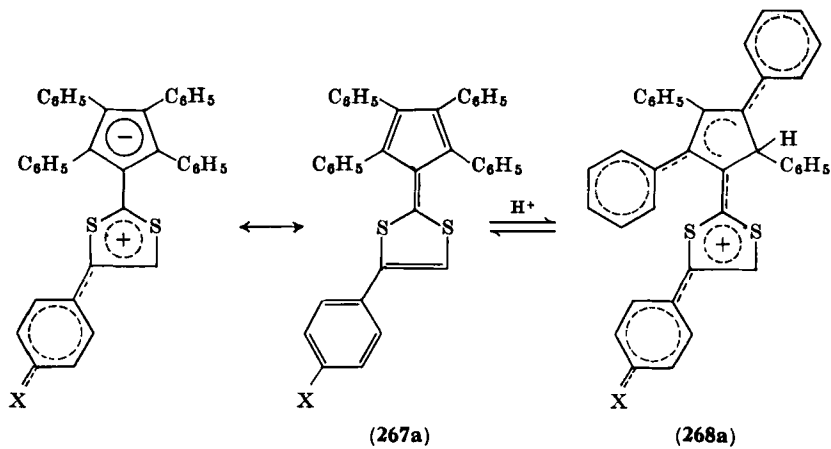
<sup>d</sup> H. Berger, Dissertation, Freiburg-im-Breisgau (1965).

<sup>e</sup> E. Campaigne and N. W. Jacobsen, *J. Org. Chem.* **29**, 1703 (1964).

<sup>f</sup> E. Campaigne, R. D. Hamilton, and N. W. Jacobsen, *J. Org. Chem.* **29**, 1708 (1964).



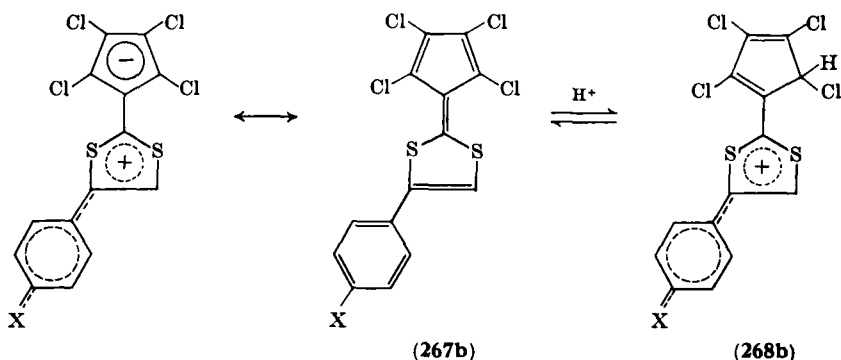
		CHCl <sub>3</sub>		CF <sub>3</sub> CO <sub>2</sub> H	
	X	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$
a	H	418; 405	25,800; 26,400	354	2940
b	OCH <sub>3</sub>	422; 406	27,200; 26,800	410	4810
c	N(CH <sub>3</sub> ) <sub>2</sub>	429	30,300	333	7400



		CHCl <sub>3</sub>		CF <sub>3</sub> CO <sub>2</sub> H	
	X	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$
a	H	455	33,100	542	19,100
b	OCH <sub>3</sub>	461	28,700	550	20,400
c	N(CH <sub>3</sub> ) <sub>2</sub>	470		553	

interpretation have already been made.<sup>1</sup> The close resemblance of the spectra of **266** to those of the analogous salts with no substituent in position 2 (Nos. 9 and 10 in Table XV) is one proof of the structure of the corresponding bases (**265**) (the difference in the position of the maxima at the longest wavelength reflects the influence of the additional alkyl residue in **266**). The relatively strong red shift of the longest-wavelength maxima of the conjugate acids of **267a** agrees with protonation in position 5 to form **268a** and with the corresponding extension of the mesomeric system of the cation<sup>154, 177</sup>

The absorption data for the conjugate acids of the tetrachloro-1,4-dithiafulvalenes (**267b**) also indicate protonation in position 5 to form **268b**.



X	CHCl <sub>3</sub>		CF <sub>3</sub> CO <sub>2</sub> H	
	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$	$\lambda_{\max}$ (m $\mu$ )	$\epsilon$
<b>a</b> H	445	41,300	470	22,400
<b>b</b> OCH <sub>3</sub>	450	34,300	496	15,400

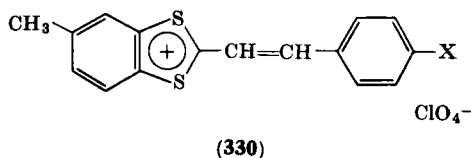
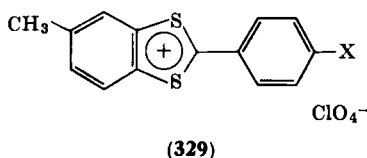
In the spectra of the bases (**265**), (**267a**), and (**267b**), on the other hand, the methoxyl group causes only a slight bathochromic shift of the maximum at the longest wavelength, as compared with a shift of

<sup>177</sup> A. Lüttringhaus, H. Berger, and H. Prinzbach, *Tetrahedron Letters* **25**, 2121 (1965).

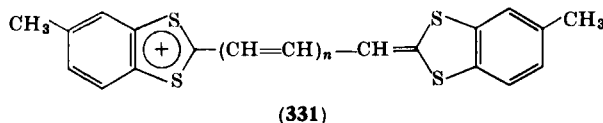
56  $m\mu$  in the case of the acid (**266**). This has been taken as a confirmation of the NMR findings (Section III, C, 4), indicating that the  $\pi$  bonds in this cross-conjugated system, which is analogous to the non-alternant bond type of sesquifulvalene, are also largely localized, so that there should be little polarization of the molecule towards the betaine structure with two "aromatic" sextets.<sup>151, 154</sup>

The intense colors of compounds 3-6 (Table XV) are attributed to the pronounced charge separation due to resonance between the dithiolium and quaternary ammonium-dithiole limiting structures.<sup>23</sup> Corresponding to this interpretation, the band observed at 515-540  $m\mu$  in weakly acidic media suffers a blue shift to 375-390  $m\mu$  in 70% perchloric acid (the dimethylamino group is fully protonated).

Even more impressive is the effect of the auxochromic substituents on the longest-wavelength maximum in the case of the fused-ring color salts (**329**) and their vinylogs (**330**); the dimethylamino group



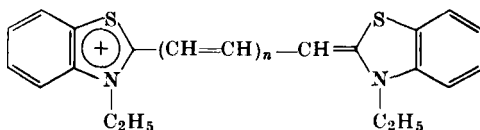
		CH <sub>3</sub> CO <sub>2</sub> H	CH <sub>3</sub> CO <sub>2</sub> H
X		$\lambda_{\max}$ (m $\mu$ )	$\lambda_{\max}$ (m $\mu$ )
<b>a</b>	H	388	446
<b>b</b>	OCH <sub>3</sub>	440	512
<b>c</b>	N(CH <sub>3</sub> ) <sub>2</sub>	536	644



CH<sub>3</sub>CO<sub>2</sub>H  $\lambda_{\max}$  (m $\mu$ ) = 514 for  $n=0$ ; 666 for  $n=1$

causes a bathochromic shift of 148  $m\mu$  in the case of the 2-phenyl-dithiolium system, and this shift is increased to 198  $m\mu$  in the styryl system.<sup>132</sup>

The replacement of the  $\text{NC}_2\text{H}_5$  group of the conventional benzo-thiazolium cyanines (**332**) by S to give the methine color salts (**331**) results in a strong bathochromic shift of about 90–110  $\text{m}\mu$ .<sup>136</sup>



(332)

$\text{CH}_3\text{COOH } \lambda_{\text{max}} (\text{m}\mu) = 423 \text{ for } n=0; 557 \text{ for } n=1$

#### 4. NMR Data

According to the molecular diagrams of the 1,3-dithiolium ion shown in Fig. 5 (Section III, C, 1), the relative electron density on C-2 is appreciably less than that on C-4 or C-5. In qualitative agreement with these theoretical findings, the H-2 signals (which appear as doublets owing to coupling with H-5 extending over four bonds) of the 4-aryl derivatives (Nos. 1 and 2 in Table XVI) lie about 2 ppm to low field of the H-5 signal. The best model available for comparison is the nonplanar diphenyldithiadene (**338**), in which the environment of the reference proton is as nearly as possible the same, and in which the bonds are as nearly as possible localized. In comparison with the chemical shifts of the equivalent protons in this model,<sup>178</sup> the H-5 signals in the 4-aryldithiolium derivatives show a paramagnetic shift of 2.6–2.7 ppm. The reasons proposed for this shift on the basis of a purely formal discussion included (in addition to the solvent effect) the ring current, which cannot at present be reliably estimated, and above all the partial electron deficiency on C-5, as symbolized by the decet (**334**) and long-bond (**335**) structures (Section III, C, 1).<sup>154</sup>

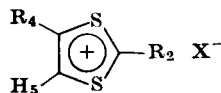
The slight but reproducible diamagnetic shift of H-2 (0.12 ppm) on introduction of the methoxyl group (+M, -I) in the remote *p*-position of the phenyl substituents (Nos. 1 and 2) has been interpreted on the basis of the limiting structures **336** and **337**. A *pd* conjugation<sup>179</sup> must be taken into account in a detailed quantum mechanical treatment of the 1,3-dithiolium system.<sup>180</sup>

<sup>178</sup> "Varian Spectra Catalog," Varian Ass., Palo Alto, 1963, Vol. 2, No. 651.

<sup>179</sup> G. Cilento, *Chem. Rev.* **60**, 147 (1960).

<sup>180</sup> S. Gronowitz, *Advan. Heterocyclic Chem.* **1**, 10 (1963).

TABLE XVI  
CHEMICAL SHIFTS OF 4- AND 2,4-SUBSTITUTED 1,3-DITHIOLIUM SALTS<sup>a</sup>



No.	R <sub>2</sub>	R <sub>4</sub>	X	δH-2 <sup>b</sup>	δH-5 <sup>b</sup>	Reference
1	H	C <sub>6</sub> H <sub>5</sub>	HSO <sub>4</sub> <sup>-</sup>	- 1.31 ( <i>D</i> , 2.2)	0.75 ( <i>D</i> , 2.2)	<i>c</i>
2	H	C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> (4)	HSO <sub>4</sub> <sup>-</sup>	- 1.19 ( <i>D</i> , 2.4)	0.87 ( <i>D</i> , 2.43)	<i>c</i>
3	C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub> <sup>-</sup>	—	1.00 ( <i>S</i> )	<i>d</i>
4	C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>4</sub> -Br (4)	ClO <sub>4</sub> <sup>-</sup>	—	1.03 ( <i>S</i> )	<i>d</i>
5	C <sub>6</sub> H <sub>4</sub> -N(CH <sub>3</sub> ) <sub>2</sub> (4)	C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> (4)	ClO <sub>4</sub> <sup>-</sup>	—	0.80 ( <i>S</i> )	<i>d</i>
6	Fluorenyl	C <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	1.26 ( <i>S</i> )	<i>c</i>
7	Fluorenyl	C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> (4)	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	1.35 ( <i>S</i> )	<i>c</i>
8		C <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	1.33 ( <i>S</i> )	<i>c</i>
9		C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> (4)	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	1.35 ( <i>S</i> )	<i>c</i>
10		C <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	2.12 ( <i>S</i> )	<i>c</i>
11		C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> (4)	CF <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	—	2.22 ( <i>S</i> )	<i>c</i>

12	C <sub>6</sub> H <sub>5</sub>	OH	ClO <sub>4</sub> <sup>-</sup>	—	2.07 (S)	e
13	SCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub> <sup>-</sup>	—	1.47 (S)	e
14	SCH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	CH <sub>3</sub> OSO <sub>3</sub> <sup>-</sup>	—	1.60 (S)	c
15	SCH <sub>3</sub>	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	ClO <sub>4</sub> <sup>-</sup>	—	1.27 (S)	e
16	SCH <sub>3</sub>	OH	ClO <sub>4</sub> <sup>-</sup>	—	4.80 (S)	e
17	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> —NO <sub>2</sub> (4)	ClO <sub>4</sub> <sup>-</sup>	—	2.27 (S)	f
18	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> —Cl (4)	ClO <sub>4</sub> <sup>-</sup>	—	2.59 (S)	f
19	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	ClO <sub>4</sub> <sup>-</sup>	—	2.63 (S)	f
20	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> —CH <sub>3</sub> (4)	ClO <sub>4</sub> <sup>-</sup>	—	2.70 (S)	f
21	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	ClO <sub>4</sub> <sup>-</sup>	—	2.75 (S)	f
22	N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> —OH (4)	ClO <sub>4</sub> <sup>-</sup>	—	2.78 (S)	f
23	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	ClO <sub>4</sub> <sup>-</sup>	—	3.90 (Q, 2.0)	f
24	N(CH <sub>3</sub> ) <sub>2</sub>	OH	ClO <sub>4</sub> <sup>-</sup>	—	5.08 (S) <sup>11</sup>	e

<sup>a</sup> Spectra measured in trifluoroacetic acid.

<sup>b</sup> In  $\tau$  values (TMS = 10); in parentheses multiplicity and coupling constants (cps).

<sup>c</sup> Dissertation H. Berger, Freiburg-im-Breisgau (1965).

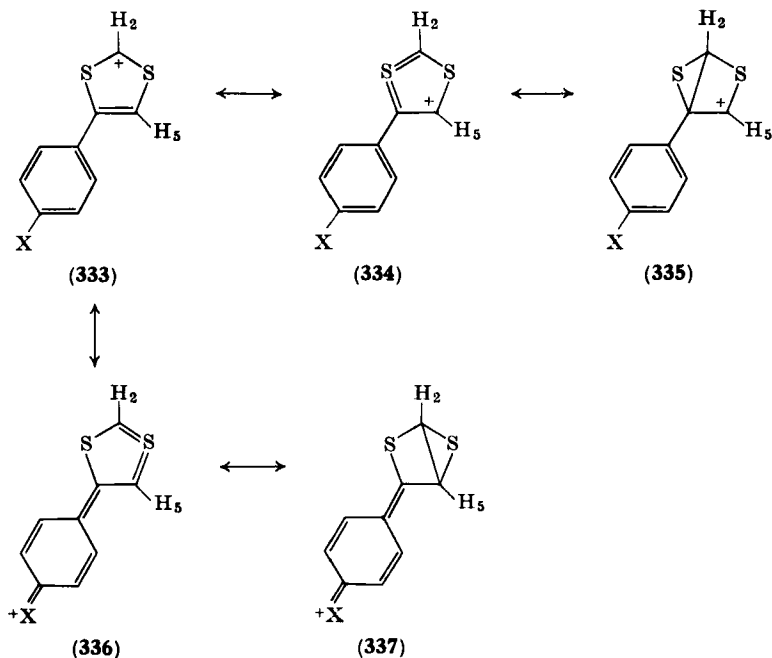
<sup>d</sup> E. Campaigne and R. D. Hamilton, *J. Org. Chem.* **29**, 1711 (1964).

<sup>e</sup> E. Campaigne, R. D. Hamilton, and N. W. Jacobsen, *J. Org. Chem.* **29**, 1708 (1964).

<sup>f</sup> E. Campaigne and N. W. Jacobsen, *J. Org. Chem.* **29**, 1703 (1964).



The variation of the H-5 shifts listed in Table XVI reflects above all the different effects of the various substituents on the screening in



position 5. In the 2-dimethylamino series (Nos. 17–24), the screening action of the electron-donating substituents increases in the order  $\text{OH} > \text{OCH}_3 > \text{CH}_3 > \text{H} > \text{Cl}$ , whereas the nitro group, as expected, decreases the screening. The very pronounced screening of H-5 in the 2-dimethylamino derivatives as compared with the alkyl- or aryl-1,3-dithiolium salts points to the small partial positive charge in position 5, and hence to a much smaller contribution of the 1,3-dithiolium structure to the resonance hybrid.

On the basis of this charge distribution, these compounds [cf. the discussion of the fused-ring analogs (Section III, A, 1, a) and of the “3,5-diamino-1,2-dithiolium salts” (Table XI)] should be regarded as salts of 2-imino-1,3-dithiole rather than as 1,3-dithiolium salts.



Model **338** was also used to obtain a rough qualitative estimate of the charge distribution of the 1,3-dithiole derivatives shown in Scheme 12, on the basis of the chemical shifts of the various H-5 signals. The fact that  $\delta\text{H-5}$  in **339** differs only slightly from  $\delta\text{H}$  in model **338** leaves no room for much contribution from a zwitterionic form. As expected,<sup>181</sup> the paramagnetic shift of the H-5 signals in the "methides" (**265** and **267a**) from the reference value of 3.47 is even smaller; i.e., the bonds seem fairly rigidly localized. The comparatively weaker screening of H-5 in **267b** points to a slight polarization which cannot be determined quantitatively. This effect is understandable in view of the high acidity of tetrachlorocyclopentadiene, in which the cyclopentadiene anion is additionally stabilized by the chlorine substituents.

The structures given for the conjugate acids (**266**), (**268a**), and (**268b**) of the 1,4-dithiafulvalenes (Nos. 6–11 in Table XVI) are also based on the relationship between the local  $\pi$ -electron distribution and the chemical shift.

As 2-alkyl-4-aryl-1,3-dithiolium derivatives, the acids (**266**) (Nos. 3 and 4) and the salts with similar substituents in position 4 (Nos. 1 and 2) have comparable (though slightly higher in **266**, owing to the alkyl group in position 2) electron densities on C-5, and hence also very similar  $\delta\text{H-5}$  values.

The strong diamagnetic shift of the  $\delta\text{H-5}$  values in the case of the tetraphenyl-substituted acids (**268a**) (Nos. 10 and 11) indicates increased screening at C-5, and hence an effective decrease in the partial positive charge; the electron deficiency must therefore be effectively delocalized over the cyclopentadienyl residue in the conjugate acid, as indicated in **268a**. On the evidence of  $\delta\text{H-5}$  alone (the screening indicates a charge distribution practically identical to that in **266**), protonation of the tetrachloro compounds (Nos. 8 and 9), as in **266**, would be expected to occur in position 9. Electronic absorption measurements, however, strongly indicate attack by the proton in position 5 to form **268b**.

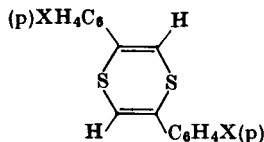
According to the low  $\delta\text{H-5}$  value, however, the positive charge is

<sup>181</sup> The dipole moments of the analogous dibenzo- and tetraphenyl-sesquifulvalenes<sup>182</sup> are essentially smaller than those of the tropones. There is effectively no ring current in pyridone-2-methide, while 2-pyridone is said to have about 25% of the aromaticity of benzene.<sup>183</sup>

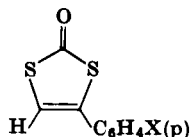
<sup>182</sup> H. Prinzbach and D. Seip, *Ann.* (in press).

<sup>183</sup> J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* p. 859 (1961).

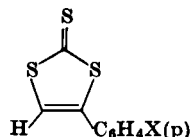
largely concentrated on the hetero ring. The tetrachlorocyclopentadienyl group, unlike the tetraphenylcyclopentadienyl group in **268a**, does not apparently take much part in the mesomerism of the system.



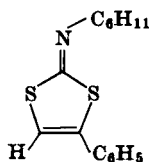
X = H: 3.47<sup>a</sup>  
 = OCH<sub>3</sub>: —  
 (338)



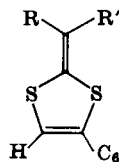
3.26<sup>b</sup>  
 —  
 (339)



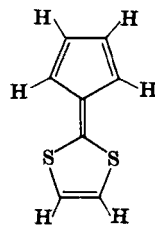
3.01<sup>b</sup>  
 3.13<sup>b</sup>  
 (340)



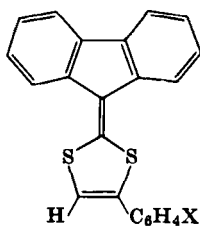
3.50<sup>c</sup>



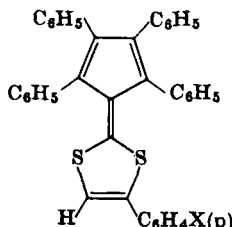
R = H; R' = COC<sub>6</sub>H<sub>5</sub>: 3.17<sup>a</sup>  
 R = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>; R' = CN: 2.96<sup>a</sup>  
 R = CN; R' = CN: 2.06<sup>a</sup>



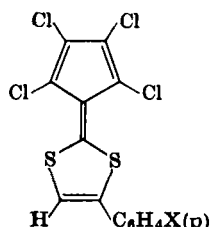
3.40<sup>a</sup>



X = H: 3.36<sup>e</sup>  
 = OCH<sub>3</sub>: 3.46<sup>e</sup>  
 = N(CH<sub>3</sub>)<sub>2</sub>: 3.52<sup>b</sup>  
 (265)



3.35<sup>f</sup>  
 3.39<sup>f</sup>  
 3.48<sup>f</sup>  
 (267a)



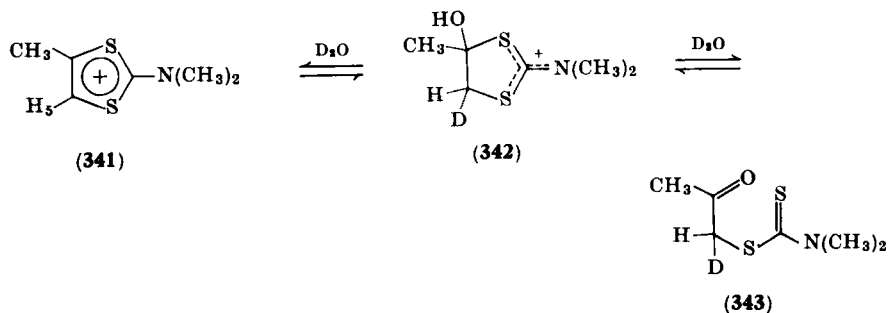
3.15<sup>e</sup>  
 3.26<sup>e</sup>  
 —  
 (267b)

H-5 chemical shift ( $\tau_{\text{TMS}}=10$ ) of 4-aryl-1,3-dithiol-2-one derivatives (ca. 5–10% w/v) <sup>a</sup>CDCl<sub>3</sub>; <sup>b</sup>CS<sub>2</sub>; <sup>c</sup>CCl<sub>4</sub>; <sup>d</sup>DMSO-d<sub>6</sub>; <sup>e</sup>C<sub>4</sub>Cl<sub>6</sub>; <sup>f</sup>C<sub>2</sub>Cl<sub>4</sub>.

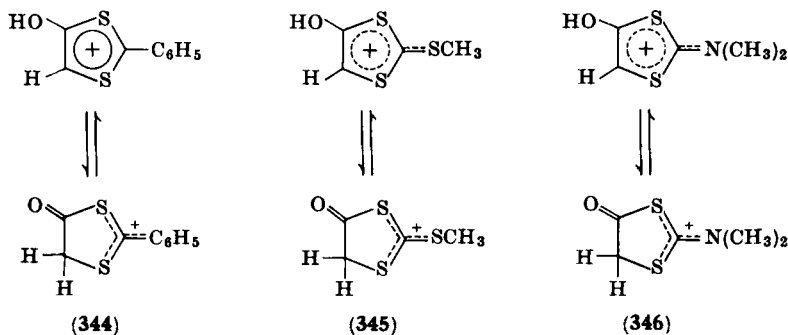
SCHEME 12

Campaigne *et al.* used NMR spectroscopy to follow the exchange of H-5 in 2-dimethylamino-4-methyl-1,3-dithiolium perchlorate (**341**) with deuterium in 10% perchloric acid/D<sub>2</sub>O. The ease with which the

exchange proceeds was explained by reversible hydration (to **342**) and hydrolysis (to **343**), followed by elimination of water and recyclization.<sup>146d</sup>



Of the three 4-hydroxy-1,3-dithiolum derivatives (**344**), (**345**), and (**346**), the 2-phenyl derivative (**344**) gives the long-wave absorption typical of alkyl and aryl derivatives in the UV region; **345** and **346**, on the other hand, do not absorb in this region (Table XV). In agreement with these findings, the H-5 NMR signal of **344** (No. 12 in Table XVI) shows conclusively that this is in fact a 4-hydroxy-1,3-dithiolum derivative. This olefinic signal is absent, however, from the NMR spectra of the perchlorates **345** and **346** in trifluoroacetic acid or 70%



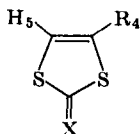
perchloric acid; these spectra contain instead a 2-proton signal in the methylene region (Nos. 16 and 24 in Table XVI). Thus these salts, both of which contain donor substituents in position 2, exist mainly in the keto form in these solvents.<sup>146e</sup> It appears, therefore, that the salts owe little stabilization energy to the formation of the  $\pi$ -electron

sextet of the 1,3-dithiolium system by enolization and entrainment of the C-4=C-5 double bond into the mesomeric system.

NMR measurements in neutral and strongly acidic media have also led to some qualitative information regarding the basicities of the "isotrithiones" and the "isodithiones" (Table XVII).

TABLE XVII

CHEMICAL SHIFTS OF "ISODITHIONES" (X=O) AND  
"ISOTRITHIONES" (X=S) IN CS<sub>2</sub> AND CF<sub>3</sub>CO<sub>2</sub>H<sup>a</sup>

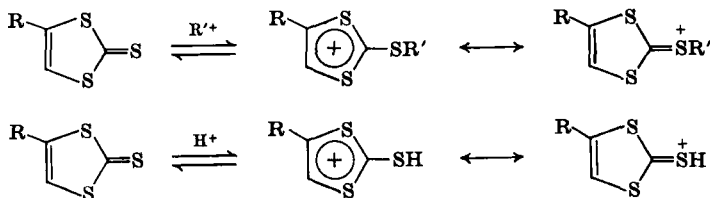


No.	R <sub>4</sub>	X	δH-5(CS <sub>2</sub> ) <sup>b</sup>	δH-5(CF <sub>3</sub> CO <sub>2</sub> H)
1	C <sub>6</sub> H <sub>5</sub>	O	3.26 (S)	3.00 (S)
2	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	O	3.48 (S)	3.08 (S)
3	C <sub>6</sub> H <sub>5</sub>	S	3.01 (S)	2.65 (S)
4	C <sub>6</sub> H <sub>4</sub> —OCH <sub>3</sub> (4)	S	3.13 (S)	2.75 (S)
5	CH <sub>3</sub>	S	3.25 (Q, 1.5)	3.02 (Q, 1.5)
6	H	S	2.80 (S)	2.47 (S)

<sup>a</sup> Data are taken from H. Berger, Dissertation, Freiburg-im-Breisgau (1965).

<sup>b</sup> In τ units (TMS = 10); in parentheses multiplicity and coupling constants (cps).

It was pointed out in Section III, A, 2, c that "isotrithiones" can be readily alkylated to form "isotrithionium salts." The relatively low δH-5 value of the "4-phenylisotrithionium salts" (No. 13 in Table XVI) indicates an effective partial charge in position 5, so that the electron distribution in these "isotrithionium salts" is more accurately represented by the 1,3-dithiolium structure than by the mesomeric sulfonium structure.



Since the  $-I$ ,  $+M$  effects of the alkylmercapto and mercapto groups are very similar in magnitude,<sup>180</sup> a very similar  $\delta H$  value must be expected for the analogously substituted and protonated "isotrithione." However, the value found for H-5 in trifluoroacetic acid ( $\tau = 2.65$ , No. 3 in Table XVII) is much higher, and differs only slightly from the value in  $CS_2$ . The equilibrium in this medium between "isotrithione" and its protonated form should therefore lie predominantly on the side of the neutral molecule.

The distinction is more doubtful in the case of the "isodithiones." The high  $\tau$  value for H-5 of the 4-aryl derivatives (Nos. 1 and 2 in Table XVII) in trifluoroacetic acid certainly rules out a 1,3-dithiolium character as indicated in **245** for the protonated form; it does not, however, rule out protonation absolutely. The high value could be explained by predominance of the oxonium structure in the resonance hybrid.

# Diquinolylmethane and Its Analogs

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Munich, West Germany*

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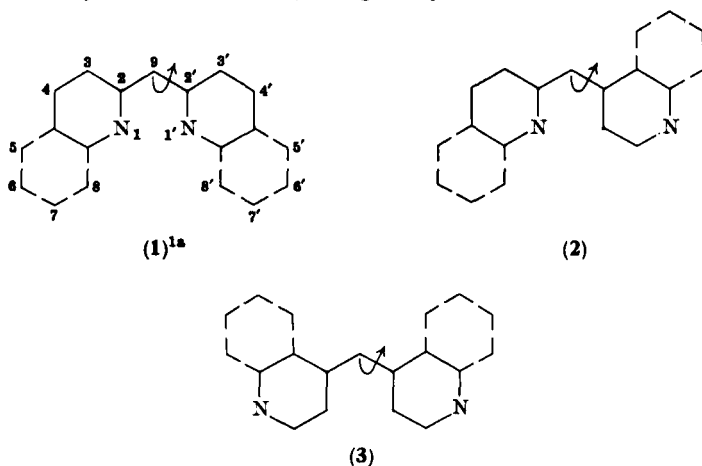
## I. Introduction

The substitution of two or three hydrogen atoms of methane by six-membered nitrogen heterocycles, like pyridine, quinoline, or benzoquinoline, leads to a class of compounds which we call *quinolylmethanes*, as its representatives are in structure as well as in their chemical and physical properties similar to di-(2-quinolyl)methane, the compound prepared first.<sup>1</sup> Substitution of the central  $-\text{CH}_2-$  (or  $=\text{CH}-$ ) bridge by  $-\text{NH}-$  (or  $=\text{N}-$ ) leads to the corresponding quinolylamines. Quinolylmethanes and quinolylamines are the fundamental substances of many cyanine dyestuffs.

In the following discussion, we confine ourselves to those compounds which are connected in the 2- or 4-positions of the heterocyclic rings.

<sup>1</sup> G. Scheibe and E. Rossner, *Ber.* **53**, 2064 (1920).

We may therefore distinguish the symmetrical 2,2'- (1) and 4,4'- (3) and the unsymmetrical 2,4'- (2) diquinolylmethanes.

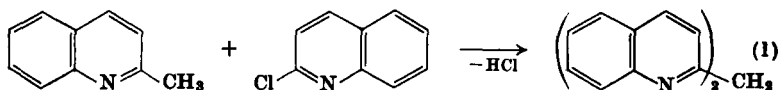


## II. Syntheses

### A. CONDENSATION REACTIONS

#### 1. Condensation of Methyl Compounds with Halogen Compounds of *N* Heterocycles

The condensation of halogen and methyl heterocycles in a 1:1 mole ratio yields di- and triquinolylmethanes simultaneously.<sup>1</sup> Using a 2:1 mole ratio, diquinolylmethanes are the main product.<sup>2-4</sup> Equation (1) indicates the formation of di-(2-quinolyl)methane.



The condensation of amino compounds with halogen derivatives to give quinolylamines proceeds similarly.<sup>5-8</sup>

<sup>1a</sup> Curved arrows indicate the possibility of rotation about the ring—C-9 bond.

<sup>2</sup> G. Scheibe, *Ber.* **54**, 786 (1921).

<sup>3</sup> G. Scheibe and G. Schmidt, *Ber.* **55**, 3157 (1922).

<sup>4</sup> G. Scheibe and H. J. Friedrich, *Ber.* **94**, 1336 (1961).

<sup>5</sup> E. Steinhäuser and E. Diepolder, *J. Prakt. Chem.* **93**, 387 (1916).

<sup>6</sup> E. Diepolder, K. Dachlauer, E. Deuerlein, and E. Wölfel, *J. Prakt. Chem.* **106**, 41 (1923).

<sup>7</sup> F. M. Hamer, *J. Chem. Soc.* **125**, 1349 (1924).

<sup>8</sup> H. H. Credner, H. J. Friedrich, and G. Scheibe, *Ber.* **95**, 1881 (1962).



The condensation proceeds via the more reactive quinaldinium salts in which the methyl groups are more activated than in the quinaldines themselves, and it is therefore necessary to add a catalytic quantity of acid to initiate the reaction.<sup>9</sup> The di- and triquinolylmethanes are separated (a) due to their different basicities by fractional crystallization of their hydrochlorides,<sup>1</sup> or (b) by precipitation of the diquinolyl compound as the zinc complex<sup>10, 11</sup> (see Section V, B, 1).

By these methods, all the sterically possible, symmetrical quinolylmethanes and quinolylamines can be prepared in good yield, with the exception of the dipyridylmethanes. However, in the synthesis of unsymmetrical quinolylmethanes difficulties arise, as the initially formed unsymmetrical compounds split up under the experimental conditions (225–300°), and the fragments recombine to the energetically more stable symmetrical forms. This applies to the synthesis of quinolylmethanes with either different<sup>12</sup> or differently substituted<sup>13</sup> heterocyclic rings. Thus, 2-quinolyl-9-phenanthridylmethane is formed from 9-chlorophenanthridine and quinaldine, or from 9-methylphenanthridine and 2-chloroquinoline, along with di-(2-quinolyl)- and di-(9-phenanthridyl)methane.<sup>14</sup> 8,8'-Dibromodi-(2-quinolyl)methane is the main product and 8-bromodi-(2-quinolyl)methane only the by-product of the reaction between 8-bromoquinaldine and 2-chloroquinoline.<sup>15</sup> 2,3-Dimethylquinoline and 2-chloroquinoline give symmetrical 3,3'-dimethyldi-(2-quinolyl)methane and unsubstituted di-(2-quinolyl)methane.<sup>13</sup> Similarly, the synthesis of 2,4'-quinolylmethanes always gives the 2,2' product as well; e.g., 4-chloroquinoline and quinaldine (2-chloroquinoline and lepidine do not react) yield di-(2-quinolyl)methane through secondary reactions, besides the 2-quinolyl-4-quinolylmethane.<sup>12</sup>

The preparation of unsymmetrical quinolylamines, e.g., 2-pyridyl-2-quinolylamine,<sup>6</sup> 2-pyridyl-9-phenanthridylamine,<sup>8</sup> and 2-quinolyl-9-phenanthridylamine,<sup>8</sup> can be performed in good yield due to the

<sup>9</sup> G. Scheibe, *Ber.* **56**, 137 (1923).

<sup>10</sup> G. Scheibe, H. J. Friedrich, W. Gückel, and H. H. Credner, *Angew. Chem.* **73**, 273 (1961).

<sup>11</sup> G. Scheibe and H. J. Friedrich, *Z. Elektrochem.* **64**, 720 (1960).

<sup>12</sup> H. Dürr, Thesis, University of Erlangen (1926).

<sup>13</sup> M. Munzer, Phys. Chem. Inst., Tech. University of Munich, private communication (1963).

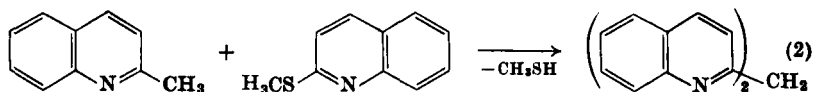
<sup>14</sup> A. Raeithel, Thesis, Tech. University of Munich (1941).

<sup>15</sup> J. van Thuijl, C. Romers, and E. Havinga, *Rec. Trav. Chim.* **83**, 1023 (1963).

greater reactivity of the starting amines allowing milder condensation conditions (about 200°).

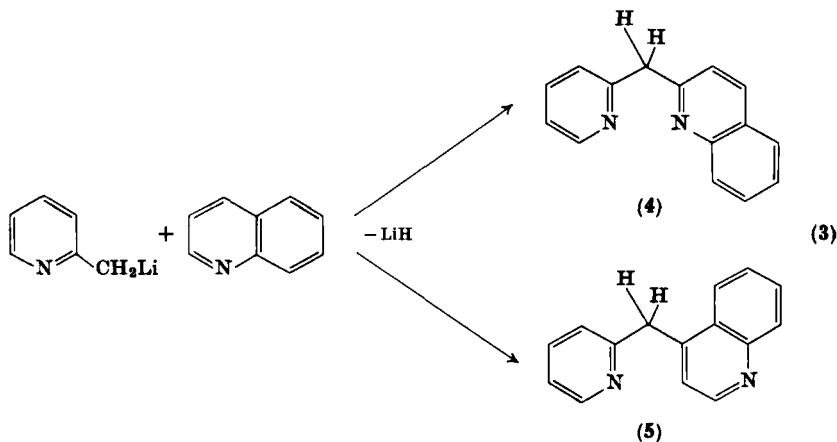
## 2. Condensation of Methylmercapto Compounds with Methyl-N Heterocycles

In contrast to the condensation described above (Section II, A, 1) which proceeds vigorously because of continuous evolution of hydrogen halide, the methylmercapto compounds can be condensed with excess of methyl derivatives of N heterocycles in a slow and mild reaction<sup>16, 17</sup>; Eq. (2) formulates this reaction for di-(2-quinolyl)-methane.



## B. PREPARATION VIA ALKALI-ORGANIC COMPOUNDS

The reaction of the alkali derivatives of  $\alpha$ -methyl-N heterocycles with the corresponding heterocyclic bases in absolute benzene or ethers<sup>16</sup> is also suitable for the preparation of the unsymmetrical products due to the milder reaction conditions. By this method, di-(2-pyridyl)methane was first synthesized from picolylolithium and



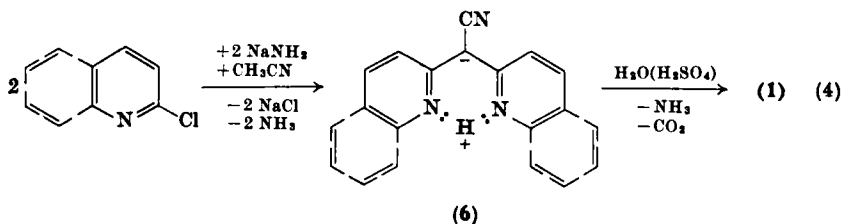
<sup>16</sup> H. J. Friedrich, W. Gückel, and G. Scheibe, *Ber.* **95**, 1378 (1962).

<sup>17</sup> A. J. Kiprianov, L. P. Yakoleva, and Y. S. Rozum, *J. Gen. Chem. USSR* **22**, 365 (1952); see *Chem. Abstr.* **46**, 11181c (1952).

pyridine by Leete and Marion.<sup>18</sup> Generally this synthesis yields 2,2'- and 2,4'-quinolylmethanes simultaneously; e.g., 2-picolyllithium and quinoline yield 2-pyridyl-2-quinolylmethane (4) and 2-pyridyl-4-quinolylmethane (5) [Eq. (3)].

### C. PREPARATION VIA MESO-CYANO COMPOUNDS

Finally there is the method for the preparation of the symmetrical di-(2-quinolyl)- and di-(4-quinolyl)methanes by which Sperber *et al.*<sup>19</sup> prepared di-(2-pyridyl)methane. By heating 2- or 4-halogen derivatives with sodamide and acetonitrile in dry toluene the 9-cyano compound is formed (6),<sup>19a</sup> and this yields the corresponding di-quinolylmethane upon refluxing with 70% sulfuric acid [Eq. (4)].



The reaction of equimolar quantities of 2-bromopyridine, 2-chloroquinoline,  $\text{NaNH}_2$ , and  $\text{CH}_3\text{CN}$  gives the symmetrical 9-cyanodi-(2-pyridyl)- and 9-cyanodi-(2-quinolyl)methanes, and *not* 9-cyano(2-pyridyl)-(2-quinolyl)-methane.<sup>20</sup>

### III. Tautomerism of Quinolylmethanes

The acidity of the central methylene bridge (C-9) leads to the formation of a second tautomeric species in most quinolylmethanes. In this way, a mesomerically stabilized colored form is produced from the colorless species with  $sp^3$  hybridization of the C-9 atom,

<sup>18</sup> E. Leete and L. Marion, *Can. J. Chem.* **30**, 563 (1952).

<sup>19</sup> N. Sperber, D. Papa, E. Schenk, and M. Sherlock, *J. Am. Chem. Soc.* **73**, 3856 (1951).

<sup>19a</sup> The colorless crystalline material obtained by Sperber *et al.*<sup>19</sup> is not identical with the yellow needles obtained by us.<sup>16</sup>

<sup>20</sup> W. Gückel, Phys. Chem. Inst., Tech. University of Munich, private communication (1961).

formally by intramolecular proton shift followed by rehybridization to  $sp^2$ .<sup>21, 22</sup>

Both forms are in equilibrium in solution. The position of the equilibrium can be determined by measurement of the extinction in the long-wavelength spectral region, which by the Lambert-Beer rule gives a direct measure of the concentration of the colored species.<sup>21-25</sup>

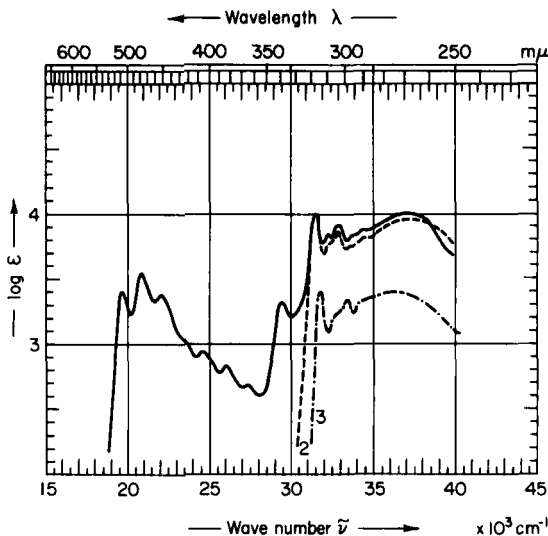


FIG. 1. Absorption spectrum of quinoline (3) in ethanol and di-(2-quinolyl)-methane: 1, after equilibrium establishment; 2, immediately after dissolution in *N,N*-dimethylformamide (pure colorless form) at 20°. In *N,N*-dimethylformamide the rate of interconversion is so low that the spectrum of the pure colorless form can be measured.

Figure 1 illustrates the results for di-(2-quinolyl)methane. Curve 1 is the absorption spectrum for the equilibrium of both forms. Curve 2

<sup>21</sup> G. Scheibe and W. Riess, *Ber.* **92**, 2189 (1959).

<sup>22</sup> Contrary to the hypothesis of Leete and Marion,<sup>18</sup> di-(2-pyridyl)-methane exists only in the colorless form.<sup>16</sup> Di-(4-pyridyl)-methane, the pyridyl-quinolylmethanes and the corresponding amines, too, do not show a second tautomeric form in solution.

<sup>23</sup> G. Scheibe and G. Kilian, *Z. Physik. Chem., Bodenstein-Festband*, **468** (1931).

<sup>24</sup> H. J. Friedrich and G. Scheibe, *Z. Elektrochem.* **65**, 767 (1961).

<sup>25</sup> H. J. Friedrich and G. Scheibe, *Z. Elektrochem.* **65**, 851 (1961).

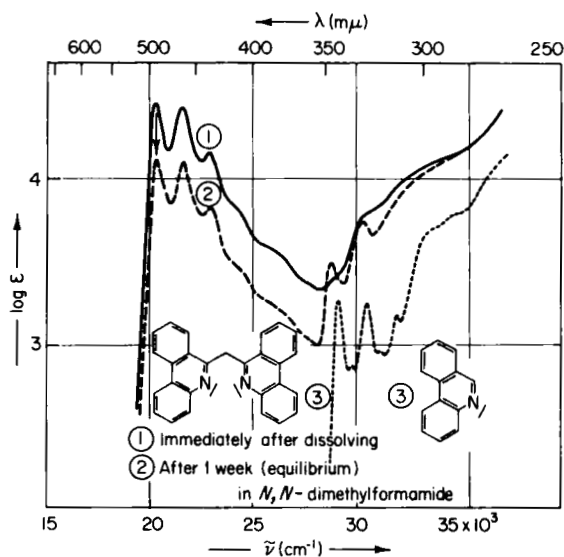


FIG. 2. Absorption spectra of phenanthridine (3) and di(9-phenanthridyl)-methane in *N,N*-dimethylformamide at 20°: 1, immediately after dissolution; and 2, after equilibrium establishment (1 week).

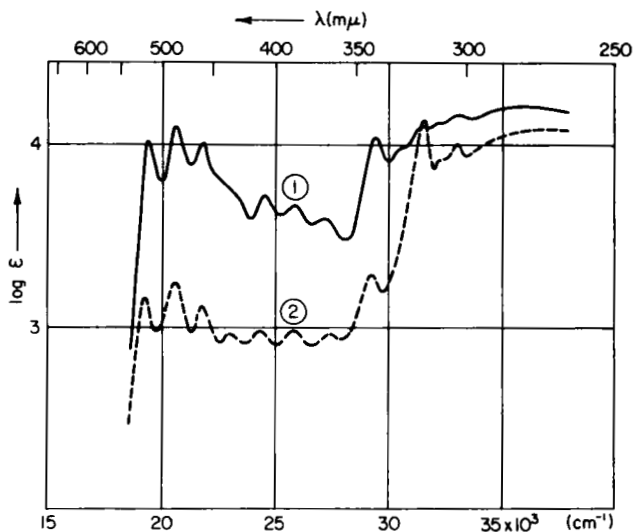


FIG. 3. Absorption spectra of 2-quinolyl-4-quinolylmethane (1) and 2-quinolyldi-(4-quinolyl)methane (2) in ethanol at 20°.

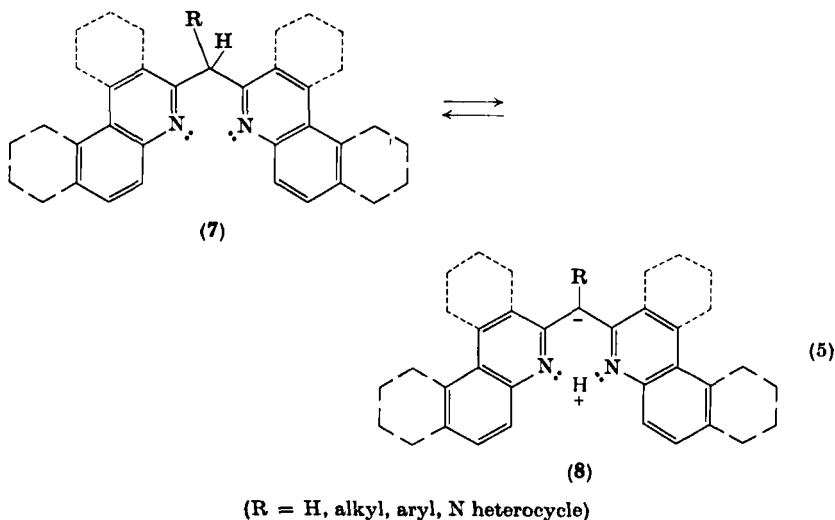
is a typical quinoline spectrum; in the colorless form the quinoline rings do not exhibit any substantial interaction. This corresponds to **7** where two quinoline rings are connected by a tetrahedral C atom which separates the  $\pi$  electron systems of the quinoline rings. Conversion into the colored form (**8**) considerably changes the spectroscopic properties; a completely new chromophoric system is formed, absorbing between 19,000 and 31,000  $\text{cm}^{-1}$ . This holds for other quinolylmethanes also (Figs. 2 and 3). Position and rate of equilibrium establishment strongly depend upon the heterocyclic rings and the solvent, as long as the rings are connected in the same manner.<sup>21, 24, 25</sup>

The prototropic changes are first order. The rate constants are remarkably small particularly for 2-quinolylmethanes [e.g., for the change colorless  $\rightleftharpoons$  colored of di-(2-quinolyl)methane in *N,N*-dimethylformamide,  $k_{40^\circ} \approx 1.10^{-4} \text{ min}^{-1}$  and  $E_A \approx 15 \text{ kcal/mole}$ ]. Especially small rate constants are found for di-(9-phenanthridyl)methane in aliphatic hydrocarbons, *N,N*-dimethylformamide, or benzene as solvents.

#### A. 2-QUINOLYLMETHANES

##### 1. The Structure of the Colored Form

The colored form of the 2-quinolylmethanes has a pure *di-cis* structure resulting in a ring formed by an intramolecular N—H...N bridge (**8**).



This constitution has been proved by various methods: by X-ray analysis of di-(9-phenanthridyl)methanes<sup>24, 26</sup> and 8-bromodi-(2-quinolyl)methane,<sup>15</sup> by the magnitude of the oscillator strength of quinolylmethanes which are entirely in the colored form,<sup>25</sup> by chemical properties (neither *N*-acetyl nor *N*-nitroso derivatives could be prepared<sup>1</sup>) and by infrared data which failed to indicate a normal

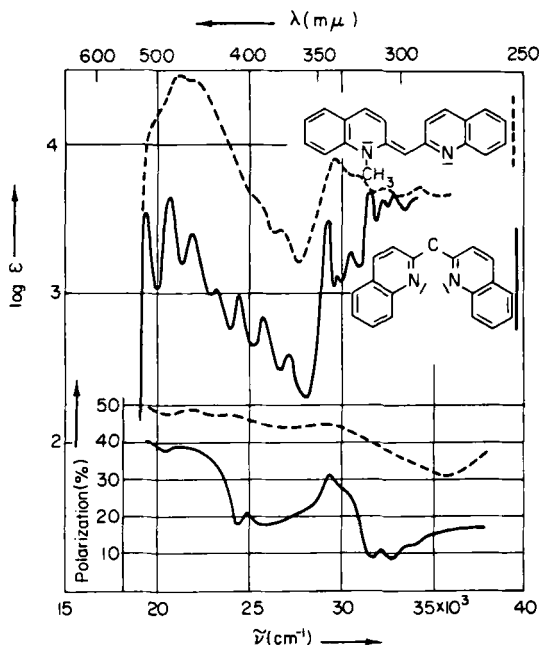


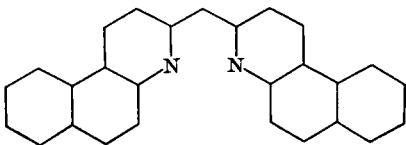
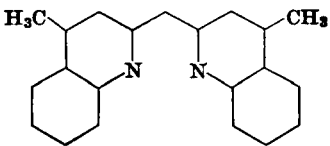
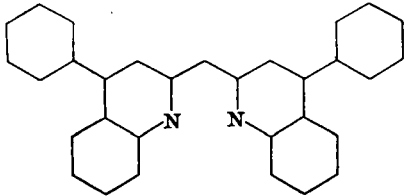
FIG. 4. Absorption and polarization spectra of di-(2-quinolyl)methane in methylocyclohexane:isopentane (2:1) (—) and its *N*-methyl base in ethanol (----) at  $-180^{\circ}$ .

N—H bond,<sup>21</sup> by the determination of the degree of polarization of the absorption bands, etc. By measuring the degree of polarization,<sup>27</sup> the four vibrational bands at the long-wavelength end and the succeeding three bands can be assigned to two perpendicularly polarized

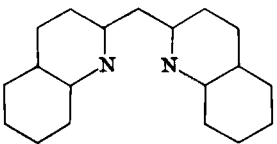
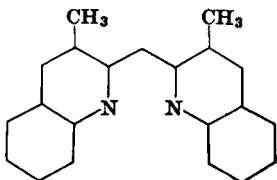
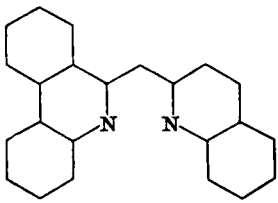
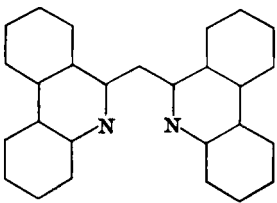
<sup>26</sup> W. Hoppe and H. Poppe, Phys. Chem. Inst., Tech. University of Munich, private communication (1963).

<sup>27</sup> Measurements of the polarization of the absorption give the relative positions of the oscillators within the molecule. For experimental details see F. Dörr and M. Held, *Angew. Chem.* **72**, 287 (1960).

TABLE I  
THE SOLVENT DEPENDENCE OF THE TAUTOMERIC EQUILIBRIUM [Eq. (5)] OF DI-(2-QUINOLYL)METHANES<sup>a</sup>

						
	$\log \epsilon_{\max}^b$	$\Delta G_0$ (kcal/mole) <sup>c</sup>	$\log \epsilon_{\max}$	$\Delta G_0$ (kcal/mole)	$\log \epsilon_{\max}$	$\Delta G_0$ (kcal/mole)
Ethanol	—	—	2.11	+ 3.2	1.94	+ 3.4
CHCl <sub>3</sub>	—	—	2.47	+ 2.6	—	—
Dioxane	—	—	—	—	—	—
CCl <sub>4</sub>	—	—	3.26	+ 1.5	3.25	+ 1.7
DMF	2.37	+ 2.8	3.40	+ 1.3	—	—
<i>n</i> -Heptane	—	—	3.60	+ 1.0	3.57	+ 1.1
CS <sub>2</sub>	—	—	—	—	3.72	+ 0.8



								
	log $\epsilon_{\max}$	$\Delta G_0$ (kcal/mole)	log $\epsilon_{\max}$	$\Delta G_0$ (kcal/mole)	log $\epsilon_{\max}$	$\Delta G_0$ (kcal/mole)	log $\epsilon_{\max}$	$\Delta G_0$ (kcal/mole)
Ethanol	2.22	+ 3.0	3.0	+ 1.9	3.30	+ 1.6	—	—
CHCl <sub>3</sub>	2.80	+ 2.0	3.67	+ 0.9	—	—	—	—
Dioxane	3.38	+ 1.4	—	—	4.02	+ 0.2	4.25	0.0
CCl <sub>4</sub>	3.40	+ 1.3	4.03	+ 0.2	3.83	+ 0.8	4.40	- 0.3
DMF	3.50	+ 1.1	—	—	—	—	4.15	+ 0.3
n-Heptane	3.63	+ 1.0	4.22	- 0.3	3.98	+ 0.5	—	—
CS <sub>2</sub>	3.79	+ 0.7	4.24	- 0.4	—	—	4.57	(- 2.0)

<sup>a</sup>  $T = 20^\circ$ ; log  $\epsilon_{\max}$  is given for the first electronic transition of the colored form.

<sup>b</sup> H. J. Friedrich and G. Scheibe, *Z. Elektrochem.* **65**, 851 (1961).

<sup>c</sup> The integral extinction of the first electronic transition for the 100% colored form can be estimated by analogy with compounds which possess the same chromophoric system, e.g., 9-cyanodi-(2-quinolyl)methanes or the alkali metal compounds. The exact determination of the equilibrium ratio is possible by NMR measurements.

electron transitions A and B in the molecule of the colored form. For all-*trans* and mono-*cis* configuration (*N*-methyl base, Fig. 4), no marked minima and maxima can be detected in the polarization spectrum.

Direct spectroscopic evidence for the N—H . . . N bridge is found by NMR, e.g., for 9-cyanodi-(2-pyridyl)methane the N—H proton is observed at  $-16.1$  ppm (in  $\text{CDCl}_3$ ).

## 2. *The Dependence of the Tautomeric Equilibrium on the Nature of the Heterocyclic Rings and the Solvent*<sup>28</sup>

The dependence of the equilibrium on the solvent and the nature of the rings is shown in Table I.

Comparison of different compounds in the same solvent distinctly indicates a decrease in  $\Delta G$  from left to right (Table I). This may correspond to an increase in acidity, i.e., to an increasing proportion of the colored form (8) in this direction.<sup>29</sup>

In the case of the corresponding triquinolylmethanes the acidity is greater, unless steric effects prevent a planar arrangement of the molecule (leading to loss of resonance stabilization). Thus, tri-(2-quinolyl)methane has smaller values of  $\Delta G$  in all solvents than di-(2-quinolyl)methane, while, for example, tri-(9-phenanthridyl)methane cannot exist in the colored form at all.<sup>24</sup>

The acidity of the methylene bridge in di-(2-pyridyl)methane and 2-pyridyl-2-quinolylmethane is not sufficient for the formation of the colored form (8) to a measurable extent. They can be arranged within the acidity series (Table I), however, if their complexes with zinc halides (Section V, B, 1) which are stronger CH acids and partially dissociate in basic solvents, are taken into consideration (Table II). Accordingly, 2-pyridyl-2-quinolylmethane is more acidic than di-(2-pyridyl)methane.<sup>29</sup>

Within a class of compounds, e.g. the quinolylmethanes, the energy difference  $\Delta G$  of the two forms can be correlated with the difference in the  $\pi$ -bonding energy, since, to a first approximation, the sum of the leveling energy and the difference between the solvation energies of the two forms is likely to be constant. The differences between the  $\pi$ -bonding energies calculated by the HMO method are therefore in

<sup>28</sup> E. Daltrozzo, G. Hohlneicher, and G. Scheibe, *Ber. Bunsenges. Physik. Chem.* **69**, 190 (1965).

<sup>29</sup> E. Daltrozzo and G. Scheibe, *Proc. Bunsen Symp.*, Mainz, 1963, see in *Z. Elektrochem.* **67**, 841 (1963).

TABLE II  
DEGREE OF DISSOCIATION OF CHELATE COMPLEXES OF  
DI-2-QUINOLYLMETHANES WITH ZINC HALIDES IN SOLUTION<sup>a</sup>

Solvent

Diethylamine<sup>b</sup>

*N,N*-Dimethyl-  
formamide

*N,N*-Dimethyl-  
formamide

log  $\epsilon_{0 \rightarrow 0^c}$        $\Delta G_0$   
(kcal/mole)

log  $\epsilon_{0 \rightarrow 0^c}$        $\Delta G_0$   
(kcal/mole)

log  $\epsilon_{0 \rightarrow 0^d}$        $\Delta G_0$   
(kcal/mole)

X = Cl	0.40	+ 5.5	1.90	+ 3.4	3.87	+ 0.4
X = Br	0.90	+ 4.8	2.00	+ 3.3	3.97	+ 0.3
X = I	1.60	+ 3.8	2.20	+ 3.0	4.20	0

<sup>a</sup>  $T = 20^\circ$ .

<sup>b</sup> The acidity of the complexes of di-(2-pyridyl)methane is sufficient for partial dissociation of a proton only in the more basic solvents, for example diethylamine, while the complexes of di-(2-quinolyl)methane in diethylamine are almost completely dissociated.

<sup>c</sup> W. Gückel, Phys. Chem. Inst., Tech. University of Munich, private communication (1961).

<sup>d</sup> G. Scheibe and H. J. Friedrich, *Z. Elektrochem.* **64**, 720 (1960).

agreement with the values obtained experimentally, which shows that there is an increase in acidity from dipyridyl- to diphenanthridyl-methane.<sup>28,30</sup>

The effect of substituents on the equilibrium and on the first excitation energy is well-explained by HMO calculations. For the colored form the greatest electron density occurs at C-9; therefore electrophilic substitution would be expected to occur at that position. This is confirmed by experiment (see Section IV, C).

In solvents with polar hydrogen bonds (alcohols, chloroform), the tautomeric equilibrium [Eq. (5)] lies more in favor of the colorless form than in other solvents. This is due to the formation of hydrogen

<sup>30</sup> G. Hohlneicher and G. Scheibe, Proc. Bunsen Symp. Mainz, 1963, see in *Z. Elektrochem.* **67**, 842 (1963).

bonds between these solvents and the colorless form. This shift of the equilibrium in favor of **7** is consistent with the reduced enolization of acetylacetone and acetoacetic ester in water and alcohol, compared with the extent to which it takes place in hexane and other hydrocarbons. This effect is likewise due to hydrogen bonding between the keto form and the solvent.<sup>30a</sup> This may be illustrated by the thermodynamic data for the transformation of the two forms of di-(2-quinolyl)methane (Table III). In solvents where there is no possibility for hydrogen-bond formation,  $\Delta H$  is negative: the reaction is exothermic; since, however, all  $\Delta G$  values—which alone determine the equilibrium—are positive, the negative value of  $\Delta H$  must be overcompensated by a positive entropy change  $T\Delta S$  (since  $\Delta G = \Delta H - T\Delta S$ ) (Table III).

TABLE III

THERMODYNAMIC DATA FOR THE CONVERSION OF THE TAUTOMERIC SYSTEM (COLORLESS  $\rightarrow$  COLORED) OF DI-(2-QUINOLYL)METHANE<sup>a</sup>

Solvent	$\Delta G_0$ (kcal/mole)	$\Delta H_0$ (kcal/mole)	$T\Delta S_0$ (kcal/mole)
Ethanol	+ 3.0	+ 2.3	− 0.7
CHCl <sub>3</sub>	+ 2.3	+ 2.0	− 0.3
<i>tert</i> -Butanol	+ 2.1	+ 1.6	− 0.5
Benzene	+ 1.5	− 0.1	− 1.6
CCl <sub>4</sub>	+ 1.3	− 0.4	− 1.7
DMF	+ 1.1	− 0.8	− 1.9
<i>n</i> -Heptane	+ 1.0	− 1.5	− 2.5
CS <sub>2</sub>	+ 0.7	− 2.4	− 3.1

<sup>a</sup> The energy which is added to the system is considered to be positive, and that given up by the system to be negative.

This decrease in entropy for the formation of the colored form (**8**) may be due (*a*) to the leveling of the molecule (by conjugation over the central C atom and the formation of the N—H...N bridge), and (*b*) to the fixation of the di-*cis* form in **8**, whereas in **7**, in non-hydrogen-bonding solvents, there is free rotation around the central C—C bond. In polar, hydrogen-bonding solvents, the colorless form is already stabilized as a result of hydrogen bonding with the solvent:  $T\Delta S$  is small. The  $\Delta G$  values therefore are greater;  $\Delta H$  is positive.<sup>29</sup>

<sup>30a</sup> J. B. Conant and A. F. Thompson, *J. Am. Chem. Soc.* **54**, 4039 (1932).

3. Substitution of the Hydrogen Atom at C-9 by Deuterium<sup>31</sup>

The substitution of a hydrogen atom of the methylene bridge by deuterium results in a pronounced shift in the tautomeric equilibrium [Eq. (5)], due to the difference between the zero point energies of hydrogen and deuterium. The direction of the shift proves the existence of a strong N—H...N bridge, while, on the other hand, this shift provides experimental evidence for the zero point energy.<sup>31</sup>

## B. 2-QUINOLYL-4-QUINOLYLMETHANES AND DI-(4-QUINOLYL)-METHANES

These compounds are not able to form intramolecular N—H...N bridges, yet the chromophoric system remains the same as that of

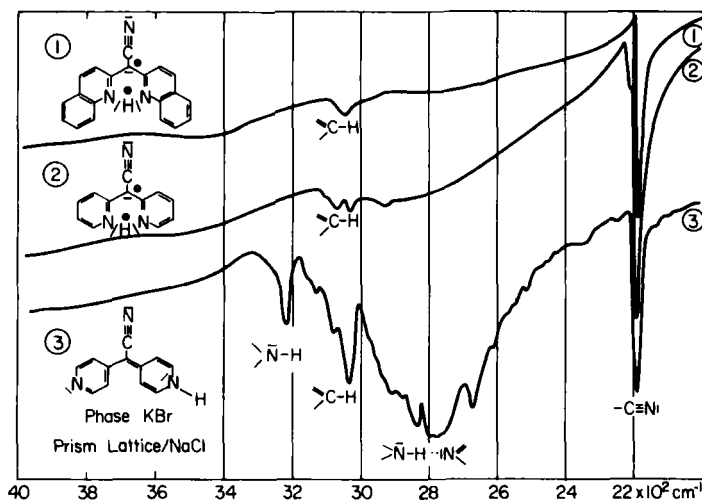
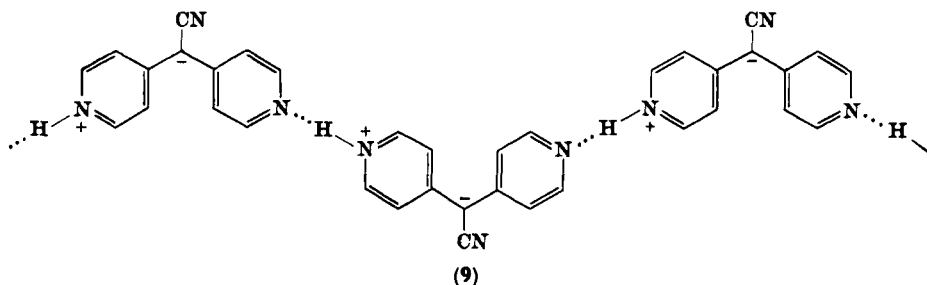


FIG. 5. Portion of the IR spectra of 9-cyanodiquinolylmethanes (in KBr).

2-quinolylmethanes (see Fig. 3). 2-Quinolyl-4-quinolylmethanes and di-(4-quinolyl)methanes exhibit the normal N—H stretching vibration at  $\sim 3400\text{ cm}^{-1}$ ; there is also indication of formation of intermolecular N—H...N bridges (Fig. 5). The molecules associate in a chainlike structure (9) in the same way as the imidazoles.<sup>32</sup> The formation of

<sup>31</sup> G. Scheibe and E. Daltrozzo, In press (1966).

<sup>32</sup> H. Zimmermann, *Z. Elektrochem.* **65**, 821 (1961).



this structure can also be detected in the UV (the UV spectrum is concentration-dependent) (Fig. 6).<sup>33</sup>

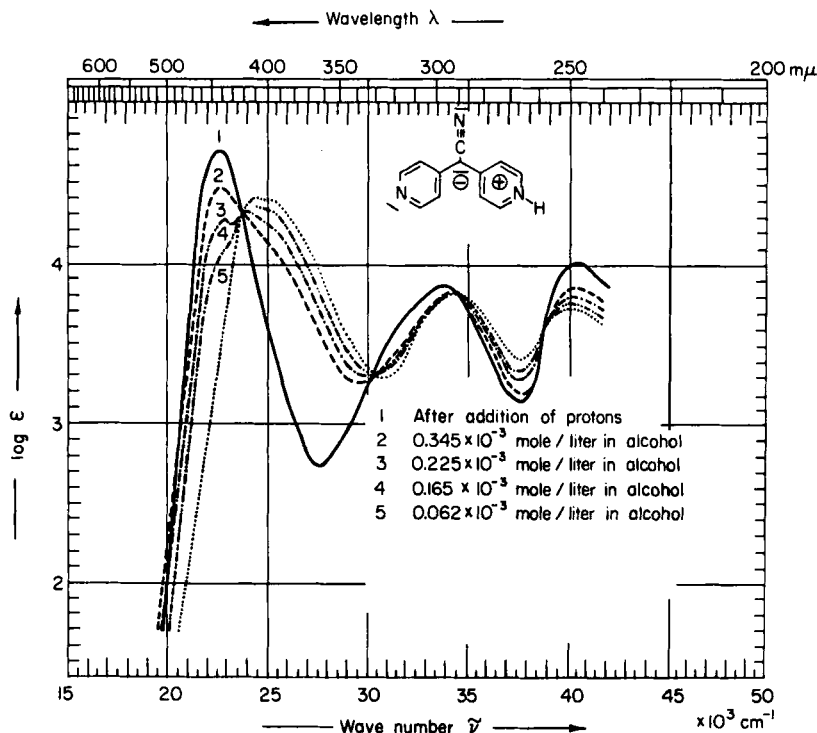


FIG. 6. Concentration dependence of the absorption spectrum of 9-cyanodi-(4-pyridyl)methane in ethanol at 20°.

<sup>33</sup> W. Gückel, Phys. Chem. Inst., Tech. University of Munich, private communication (1960).

## C. QUINOLYLAMINES

Quinolylamines, like the corresponding quinolylmethanes, exhibit tautomerism,<sup>6, 8</sup> again with the exception of the dipyridyl- and pyridylquinolyl derivatives. The tautomeric equilibrium is reached far faster with quinolylamines than with the corresponding quinolylmethanes. The position of equilibrium is again strongly dependent on the solvent and on the heterocyclic residue (see Fig. 7).

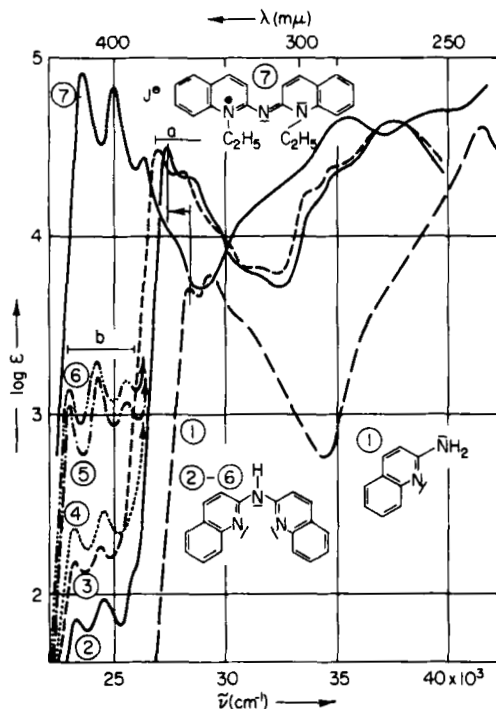
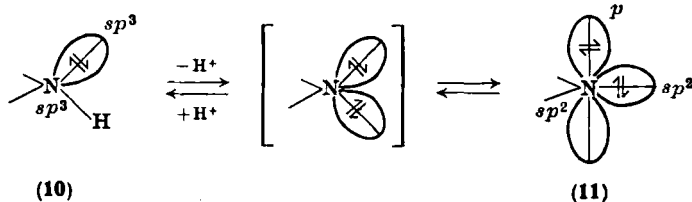


FIG. 7. Absorption spectra at 20° of 2-aminoquinoline in ethanol (1); of di-(2-quinolyl)amine at equilibrium in diethyl ether (2), in piperidine (3), in dioxan (4), in *n*-heptane (5), in  $\text{CCl}_4$  (6); and of *N,N*-diethylquinoazacyanine iodide in ethanol (7).

Di-(9-phenanthridyl)amine exists completely as the colored form in solution. It does not show absorption in the N—H region in the IR; dipyridyl- and diquinolylamine show a normal N—H band between 3300 and 3400  $\text{cm}^{-1}$ .<sup>8</sup> The unshared electron pair at the meso-N atom does not give rise to chromophoric absorption in the colorless form

(10); it can be assigned to a pyramidal, secondary amino-N atom: in the spectrum, the absorption of the aromatic ring principally remains the same, only the first absorption band is bathochromically displaced by ca.  $1000\text{ cm}^{-1}$  in comparison with 2-aminoquinoline. The shift is larger here than with quinolylmethanes ( $200\text{--}700\text{ cm}^{-1}$ ), and it may be explained by the interaction of the aromatic rings through the free electron pair of the pyramidal meso-N atom.

Dissociation results in the loss of the N-9 proton and is followed by rehybridization to give a trigonal N atom [11]. The remaining electron pair is present in a  $p$  orbital perpendicular to the plane of the molecule and gives rise, through its interaction with the  $\pi$  electrons of the aromatic rings, to the strongly solvent-dependent long-wavelength band of the colored form (11) (see Fig. 7).



The hypsochromic shift of these bands, ca.  $4000\text{ cm}^{-1}$  with respect to the corresponding methanes, is in accordance with Kuhn's rule<sup>34</sup> for the replacement of the meso-C atom by a N atom in a chromophoric system with  $4n + 2$   $\pi$  electrons.<sup>8</sup>

## IV. Reactions at C-9

### A. SALT FORMATION

Under the action of alkali metals and strong bases, such as the alkali-organic compounds, the colorless form loses a proton at C-9.

9-Substituted quinolylmethanes can be prepared by reaction of the deeply colored compounds of alkali metals with alkyl halides.<sup>18</sup>

The absorption spectra of the alkali compounds of the 2-quinolylmethanes and -amines in solvents of small polarity (see Fig. 8) show a pronounced vibrational structure<sup>35</sup> in cases where a planar arrange-

<sup>34</sup> H. Kuhn, *Chimia (Aarau)* **9**, 237 (1955).

<sup>35</sup> A marked vibrational structure in an electronic spectrum is a result of a rigid, planar structure of the molecule, in which no torsional vibrations are allowed. See further, G. Kortüm and G. Dreesen, *Ber.* **84**, 182 (1951); E. Merkel, *Naturwiss.* **34**, 122 (1947); *Z. Elektrochem.* **63**, 373 (1959).



ment of the molecule is sterically possible; the electron-excitation energy and the integrated absorption energy are dependent on the

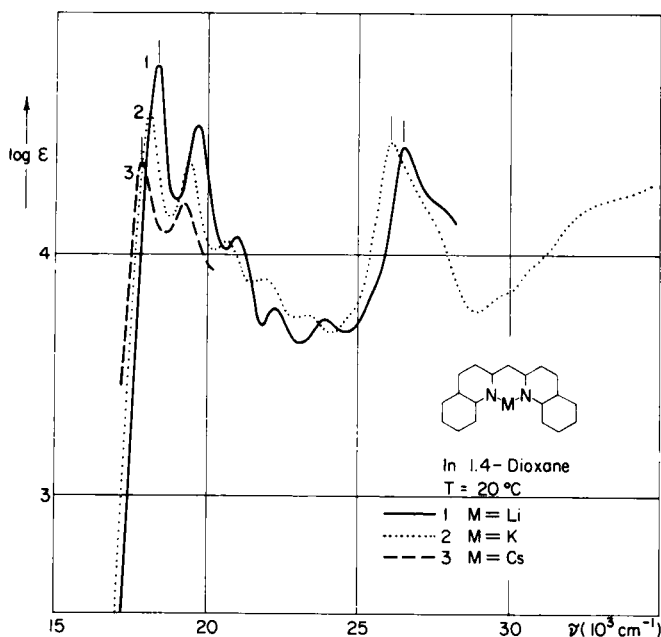
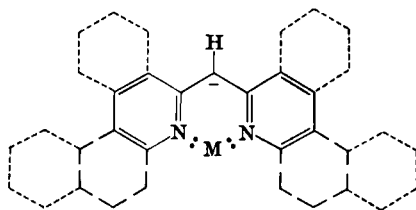


FIG. 8. Absorption spectra of di-(2-quinoyl)methyl-lithium, di-(2-quinoyl)methyl-potassium and di-(2-quinoyl)methyl-cesium in dioxane at 20°.

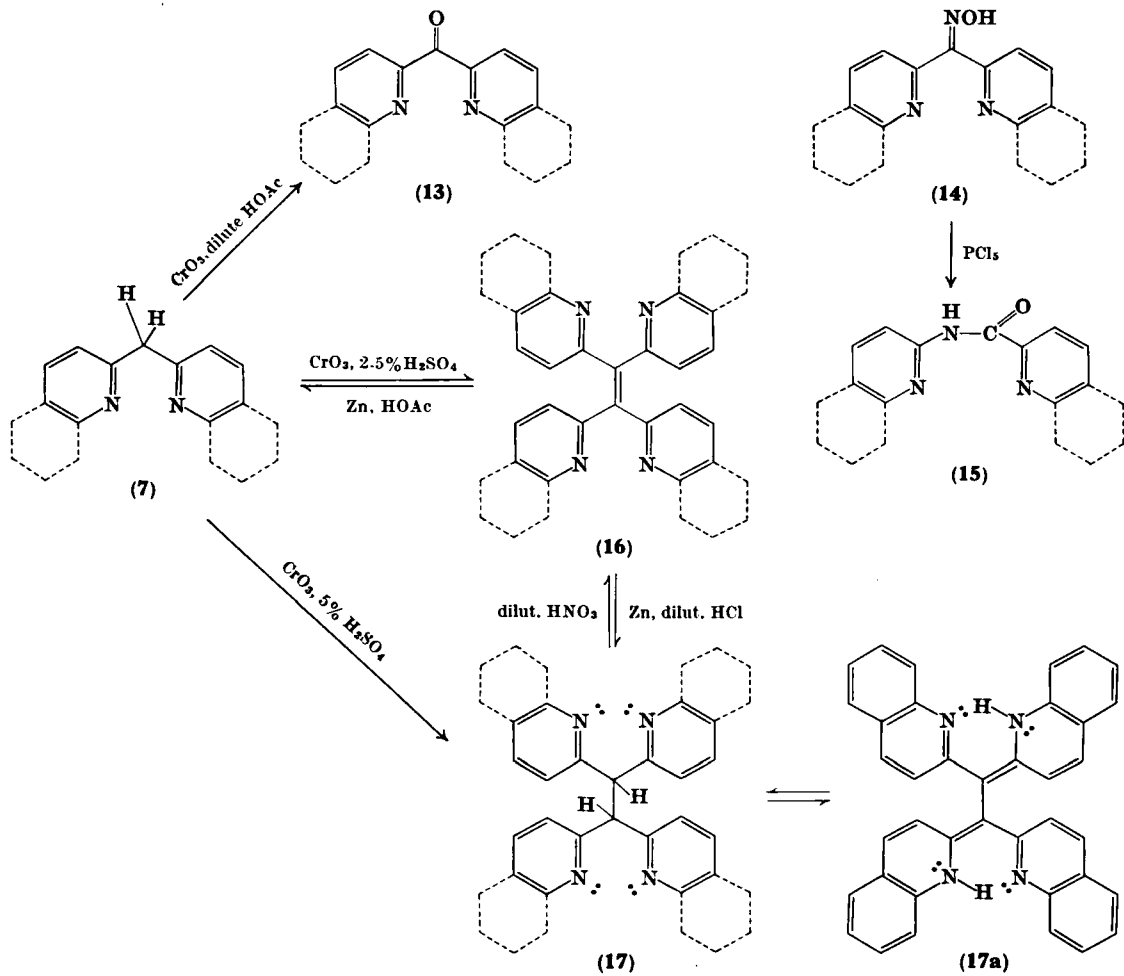
radius of the metal cation. Also, since the fluorescence spectra and oscillator strengths of these compounds indicate a closed-ring structure (12) with a (strong) fixed bond between the metal and both N atoms, they are not strictly salts<sup>36</sup> (see Section V, B).



(12)

(M = Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Cs<sup>+</sup>)

<sup>36</sup> E. Daltrozzo and G. Hohlneicher, In press (1966).



## B. OXIDATION

Diquinolylmethanes are oxidized to diquinolylketones (**13**) by air-O<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, or CrO<sub>3</sub> in acetic acid.<sup>3, 18</sup> The ketones (**13**) can also be prepared by condensation of the diquinolylmethanes with *p*-nitrosodimethylaniline, followed by hydrolysis with sulfuric acid.<sup>3, 37</sup> The ketoximes (**14**) undergo the Beckmann rearrangement, with PCl<sub>5</sub> in ether, to give amides (**15**).<sup>18</sup> On oxidation, triquinolylmethanes give the corresponding carbinols.<sup>1</sup>

Oxidation of di-(2-quinolyl)methanes with chromic acid in 5% sulfuric acid yields, besides small quantities of **13**, the tetraquinolylethanes (**17**) as main product; in 2.5% sulfuric acid the tetraquinolylethylenes (**16**) are formed, and in concentrated sulfuric acid under the same conditions (heating on a water bath) no oxidation occurs at all.<sup>38</sup> In contrast to the colorless compounds (**16**), compounds **17** are able to form the tautomeric colored species (**17a**).

The same pH dependence is observed for the reduction of **16** with zinc in acidic solution as for the oxidation of **7**: in acetic acid the reduction yields **7**, while in dilute hydrochloric acid only **17** is obtained (Scheme I).<sup>38</sup>

## C. ELECTROPHILIC SUBSTITUTION

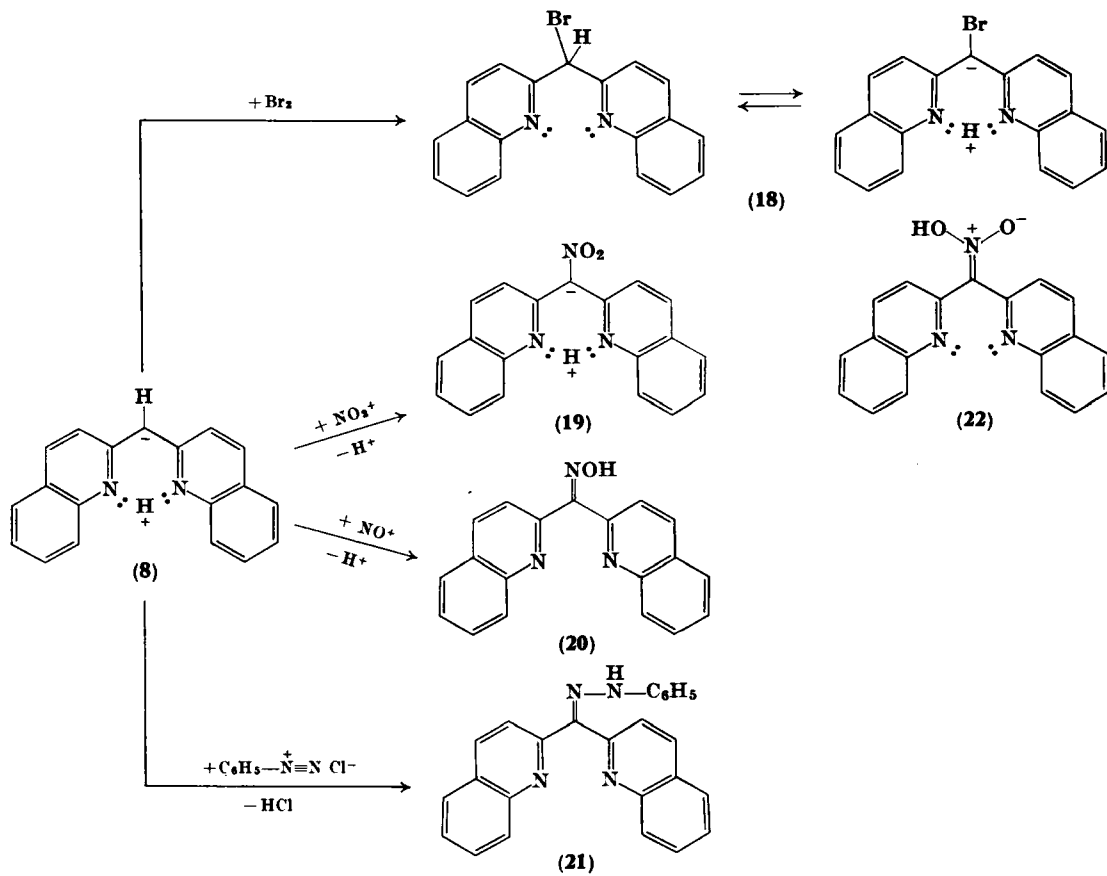
All tautomeric quinolylmethanes undergo electrophilic substitutions. They always take place at the C-9 of the colored form and are accompanied by the rearrangement of the proton in this position (Scheme II).<sup>4</sup>

If the electron density is increased at C-9, e.g., by substitution with bromine, then the equilibrium [Eq. (5)] is shifted in favor of the colorless form. A decrease in electron density, e.g., by substitution with —CN or —NO<sub>2</sub>, shifts the equilibrium in the opposite direction. Thus, 9-nitro- and 9-cyanodiquinolylmethanes exist completely in the colored form.

The reaction of bromine with triquinolylmethane yields triquinolylbromomethane, and this by the action of ethanolic KOH can be converted into the ethyl ether of the carbinol.<sup>9</sup>

<sup>37</sup> J. P. Wibaut, H. J. den Hertog, and A. P. de Jonge have prepared dipyrindylketones by the reaction of pyridyl-lithium with 2- or 4-cyano- (or 2- or 4-COOR) pyridines and other compounds; *Rec. Trav. Chim.* **70**, 1054 (1951); **70**, 989 (1951).

<sup>38</sup> E. Felger, Thesis, University of Erlangen (1926).



SCHEME II

The C—Br bond of **18** is labile and easily broken in weakly basic solvents at room temperature. Condensation of two molecules of **18** yields tetraquinolyethylene (**16**), with the elimination of two molecules of HBr.

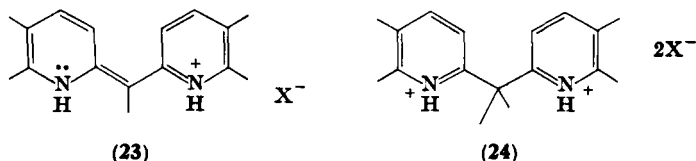
While **20** and **21** are in the oxime and hydrazone forms, **19** is in solution not in the aci form (**22**).<sup>13</sup>

## V. Reactions at the Nitrogen Atoms

### A. QUATERNIZATION

#### 1. Cyanine and Azacyanine Dyestuffs

With acids HX, colored mono or colorless di salts are formed, depending on the molecular proportion of the acid; e.g., 2-quinolylmethanes give **23** and **24**. The cationic mono salts (**23**) correspond to



dyestuffs of the pseudoisocyanine type, which are prepared by double alkylation and intermediary elimination of HX (Fig. 9).

On quaternization with alkyl halides, 2-quinolyl-4-quinolylmethanes yield isocyanines and di-(4-quinolyl)methanes the corresponding cyanines. Quinolylamines give azacyanines in an analogous way. Since cyanine dyestuffs are readily prepared by condensation of the *N*-alkyl quaternary compounds<sup>39, 40</sup> of quinolylmethanes and -amines, by reactions analogous to those described in Section II, A, 1, the method of preparation involving alkylation of the parent compounds is of little practical use.

For steric reasons, the dye salts cannot exist in the purely di-*cis* form; according to the energy of the system (depending on the position of the respective dipoles, etc.) they have the linear all-*trans* or the

<sup>39</sup> G. de W. Anderson, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, p. 1053. Elsevier, Amsterdam, 1959.

<sup>40</sup> O. Riester, in "Ullmanns Encyclopaedia of Technical Chemistry" (W. Foerst, ed.), Vol. 14, p. 310. Chem. Publications, Weinheim, 1963.

mono-*cis* configuration, as can be concluded, for example, from the greater oscillator strength of the chromophoric band.<sup>41</sup>

For the cyanine dyestuffs, a characteristic correlation exists between basicity, the sterically induced twisting of parts of the molecule out of the plane, and the electronic excitation energy.<sup>42-45</sup>

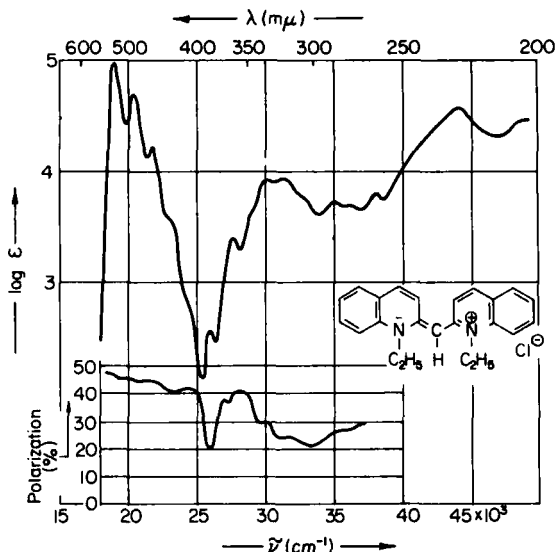


FIG. 9. Absorption and polarization spectra of *N,N*-diethylpseudoisocyanine chloride ( $10^{-4}$  mol/liter) in ethanol at  $-180^\circ$ .

## 2. Quinoline Red Dyestuffs

In the 2-quinolylmethanes and -amines, the di-*cis* configuration can be fixed by quaternization with compounds having two active atoms, e.g.,  $\text{CH}_2\text{I}_2$ .<sup>46, 47</sup> The rigid ring structures formed in this way cause the intense fluorescence of these compounds which are known as quinoline red dyestuffs (e.g., pyridine red, quinoline red, phenan-

<sup>41</sup> G. Scheibe, H. J. Friedrich, and G. Hohlneicher, *Angew. Chem.*, **73**, 383 (1961).

<sup>42</sup> G. Scheibe and D. Brück, *Z. Elektrochem.* **54**, 403 (1950).

<sup>43</sup> G. Scheibe, D. Brück, and F. Dörr, *Ber.* **85**, 867 (1952).

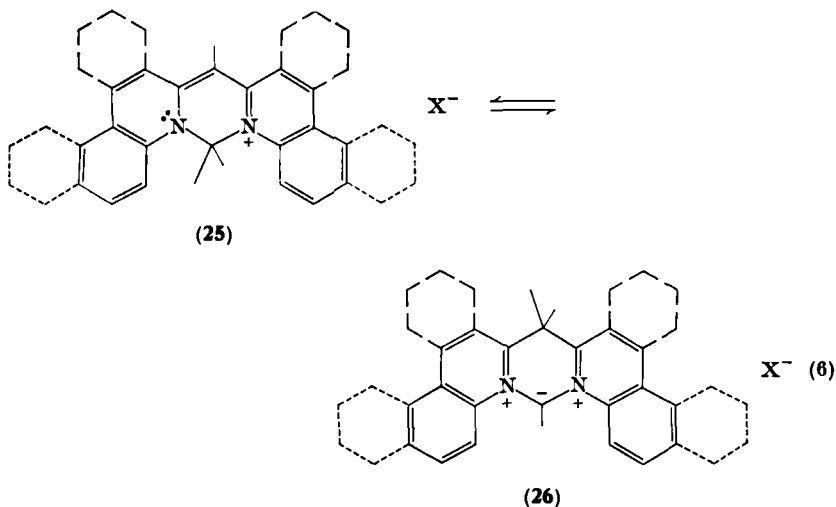
<sup>44</sup> G. Scheibe, *Chimia (Aarau)* **15**, 10 (1961).

<sup>45</sup> G. Scheibe, W. Seiffert, H. Wengenmeyer, and C. Jutz, *Z. Elektrochem.* **67**, 560 (1963).

<sup>46</sup> G. Scheibe and W. Fischer, *Ber.* **59**, 502 (1926).

<sup>47</sup> E. Daltrozzo, G. Scheibe, and J. Smits, *Chimia (Aarau)* **19**, 325 (1965).

thridine red, 5,6-benzoquinoline red, and the corresponding compounds with different heterocycles). In solution they appear in tautomeric forms [Eq. (6)]. The equilibrium lies in all known cases in favor of **25**, which absorbs at shorter wavelengths than does **26**.



In solutions of pyridine red, the equilibrium lies completely on the side of **25**.<sup>47</sup>

Figure 10 shows the absorption and polarization spectra of quinoline red. The bands corresponding to the ylidic structure (**26**) are indicated by  $\gamma$ .

Quinoline red dyestuffs which are prepared by quaternization with benzalchloride, diphenyldichloromethane, phosgene, or 1,2-dibromoethane exist only as form **25** (see Fig. 13).

## B. RING CLOSURE REACTIONS OF 2-QUINOLYLMETHANES WITH METAL COMPOUNDS

### 1. With Transition Metal Compounds

Due to the position of their free electron pairs in the colorless form, the 2-quinolylmethanes and -amines are able—in contrast to the 2,4' and 4,4' compounds—to form chelate complexes with suitable transition metal compounds. However, the formation of these complexes is dependent on sterical effects.<sup>10, 11</sup> While, for example,

di-(2-quinolyl)methane and -amine can form only tetrahedral complexes ( $\text{Zn}^{2+}$ ,  $\text{Co}^{2+}$ ), 2-pyridylmethanes and -amines can also form planar complexes ( $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ).<sup>10, 48</sup> In the presence of proton acceptors B, e.g., *N,N*-dimethylformamide or piperidine, the colorless neutral complex (27) loses a proton, and the colored anion (28) is

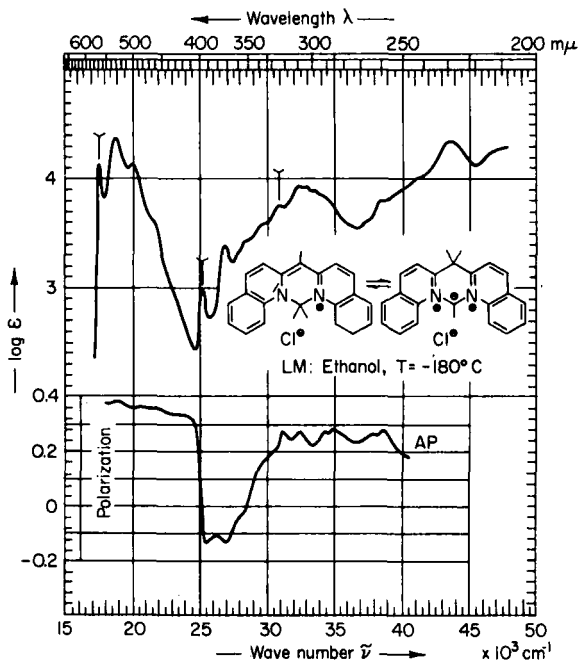


FIG. 10. Absorption and polarization spectrum of quinoline red chloride in ethanol at  $-180^\circ$ .

formed. As the basicity of B increases (*N,N*-dimethylformamide < pyridine < piperidine), the acid-base equilibrium ( $27 \rightleftharpoons 28$ ) moves from left to right, but, also, the exchange reaction leading to  $\text{B}_2\text{MX}_2$  and quinolylmethane occurs to a greater extent.<sup>11</sup>

The rate and extent of the dissociation are dependent upon the ligands of the transition metal compound (see Fig. 11 and Table II). This can be understood only if there is a covalent bond between the N atoms and the metal.<sup>11</sup>

<sup>48</sup> E. Bayer, *Angew. Chem.* **72**, 566 (1960); **76**, 76 (1964).



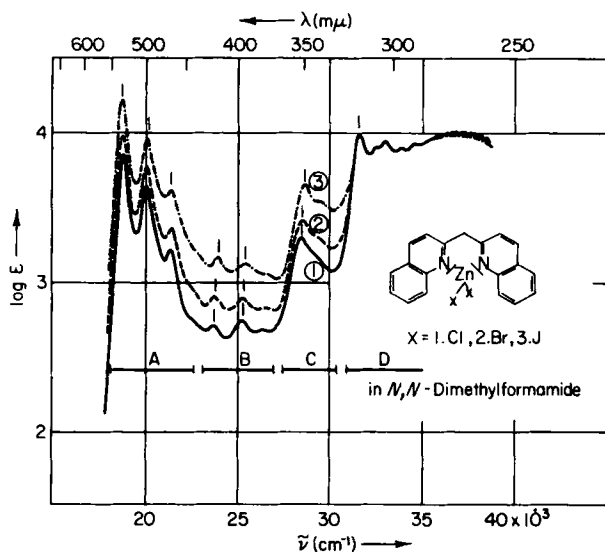
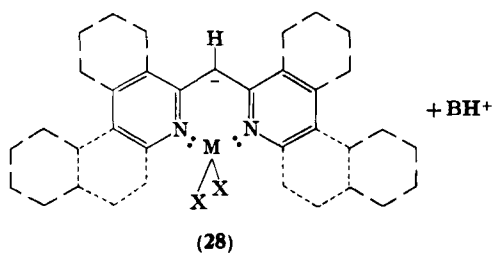
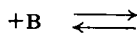
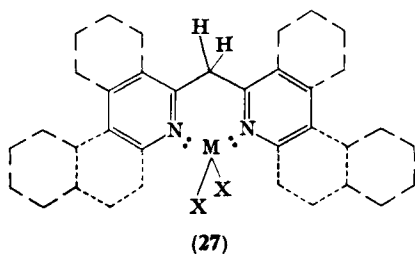


FIG. 11. Absorption spectra of zinc halide complexes of di-(2-quinolyl)-methane in equilibrium at 20° in *N,N*-dimethylformamide. A, B, C, and D denote the positions of different electronic transitions. 1, X = Cl; 2, X = Br; 3, X = I.

Di-(9-phenanthridyl)methane crystallizes in the colored form; in solution it attains equilibrium very slowly and is therefore not able, immediately after dissolving, to form chelate complexes with zinc halides, as the N—H...N bridge blocks the electron pairs of the nitrogen atoms. On addition of  $\text{ZnCl}_2$  to its solution in *N,N*-dimethylformamide, the long-wavelength band of the complex appears only after 2 days, i.e., after the change to the colorless form has begun.<sup>24</sup>

Tri-(2-quinolyl)methane does not form complexes, apparently because of steric hindrance from the third quinoline ring.<sup>10</sup> For the same reason the alkali compounds of tri-(2-quinolyl)methane possess no (direct) bond between metal and N atoms like **12**.

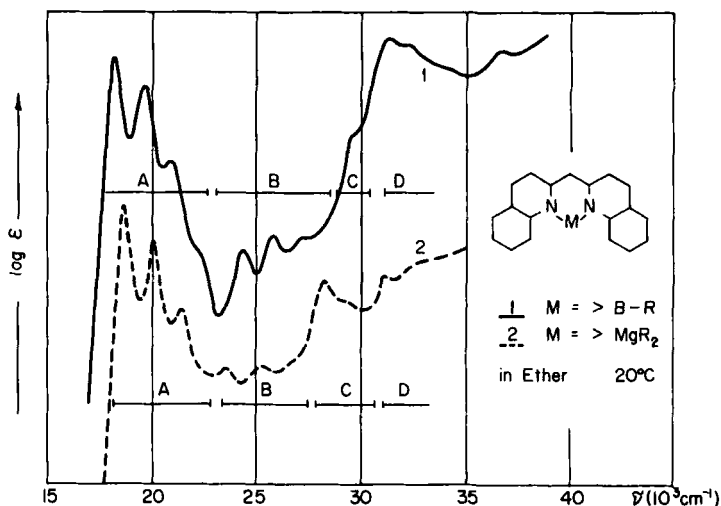


FIG. 12. Absorption spectra of the complexes of di-(2-quinolyl)methane with boron and magnesium compounds ( $R = \text{C}_6\text{H}_5$ ) in ether at 20°. A, B, C, and D denote different electronic transitions.

## 2. With Main Group Metals

Ring closure occurs also with main group metals, e.g., with suitable compounds of magnesium, boron, etc.<sup>49</sup> (Fig. 12).

## C. SUMMARY

In summary we may say that heterocyclic six-membered ring systems can be prepared with elements of Groups Ia (Section IV, A),

<sup>49</sup> E. Daltrozzo, To be published.

IIa and IIIa (Section V, B, 2), and IVa (Section V, A, 2) of the periodic system, and with transition metals (Section V, B, 1). All these metal compounds and those quinoline red dyestuffs which exist only in the form **25** by introduction of suitable substituents (e.g., Fig. 13) have analogous absorption and fluorescence spectra, with pronounced vibrational structures, and many other similar properties. This

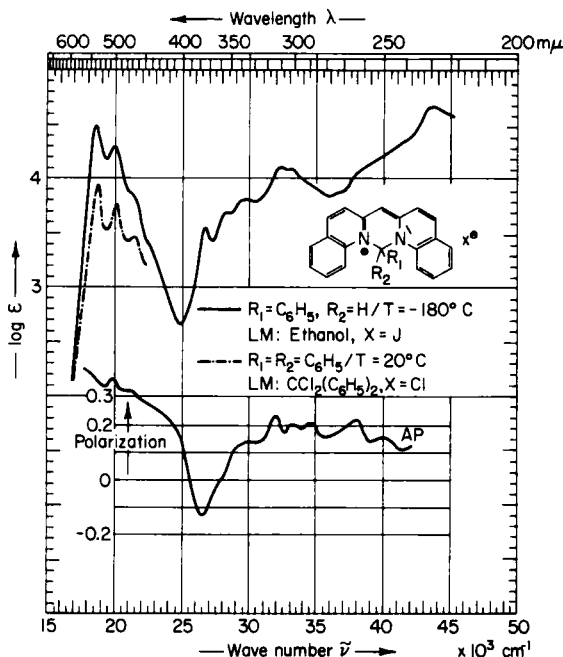


FIG. 13. Absorption and polarization spectra of quinoline red derivatives.

indicates that all these compounds with structure **12** contain a similar kind of bonding between the N atoms of the 2-quinolyl-methanes and M, where M is an alkali metal ion,  $\text{MgR}_2$ ,  $=\text{B}\cdot\text{R}$ ,  $=\text{CR}_2$ ,  $\text{ZnR}_2$ , etc., and that there is *no* cyclic conjugation over the bridge atom M.<sup>49</sup> Figures 9–13 show this for some compounds of di-(2-quinolyl)methanes. The small differences in the absorption spectra may be attributed to variations in the positive charge of the nitrogen atoms.

# Recent Advances in 1,3,4-Oxadiazole Chemistry

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## I. Introduction

This article will present a survey of the chemistry of the 1,3,4-oxadiazoles from 1958 on, and is a continuation of the previous reviews in this area.<sup>1,2</sup> Although 1,3,4-oxadiazoles have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. This is primarily due to the large

<sup>1</sup> J. H. Boyer, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 525. Wiley, New York, 1961; L. G. Behr, in "Five and Six-Membered Compounds with Nitrogen and Oxygen," Vol. 17 of "The Chemistry of Heterocyclic Compounds" (R. H. Wiley, ed.), p. 263. Wiley (Interscience), 1962.

<sup>2</sup> G. Dupont and R. Locquin, in "Traité de chimie organique" (V. Grignard, ed.), Vol. 21, p. 997. Masson, Paris, 1953; E. Hoggarth, in "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. 4A, p. 471. Elsevier, Amsterdam, 1957; E. P. Nesynov and A. P. Grekov, *Usp. Khim.* **33**, 1184 (1964).

number of uses of 1,3,4-oxadiazoles in the most diverse areas, for example in drug syntheses, scintillation materials, and the dyestuffs industry. Consequently, patents make up a large portion of the recent literature. Moreover, ring cleavage reactions of the 1,3,4-oxadiazoles have also excited great interest in various fields, since they lead to new aliphatic nitrogen-containing compounds and to other ring systems.

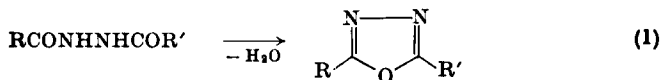
The following pages will be devoted mainly to the syntheses, the reactivity, the physical properties, and the uses of 1,3,4-oxadiazoles.

## II. Preparation of 1,3,4-Oxadiazoles

### A. PREPARATION BY RING CLOSURE OF CHAINS WITH A PREFORMED 1,3,4-OXADIAZOLE SKELETON

#### 1. Ring Closure by Means of a Condensation Reaction

a. *Condensation with Elimination of Water.* The starting materials are mono- and diacid hydrazides, acylsemicarbazides, and related compounds. The ring closure producing the oxadiazole proceeds as in Eq. (1). The well-known conversion of *N,N'*-diacid hydrazides to



2,5-diaryl(alkyl)-1,3,4-oxadiazoles has been described by Stollé<sup>1, 3</sup> who used dehydrating agents and also by Pellizzari<sup>4</sup> who employed prolonged heating above the melting point. With relatively stable substituents R or R', fuming sulfuric acid,<sup>5-9</sup> chlorosulfonic acid,<sup>10</sup> and SO<sub>3</sub>/DMF<sup>11</sup> may be used, particularly if the ring closure is to be

<sup>3</sup> R. Stollé, *Ber.* **32**, 797 (1899); *J. Prakt. Chem.* **68**, 130 (1903).

<sup>4</sup> G. Pellizzari, *Atti Reale Accad. Lincei* [5] **8**, Part I, 327 (1899).

<sup>5</sup> W. Mueller and A. E. Siegrist (Ciba), U.S. Patent 2,838,520 (1958); see *Chem. Abstr.* **52**, 17290 (1958).

<sup>6</sup> A. E. Siegrist and F. Ackermann (Ciba), U.S. Patent 2,845,419 (1958); see *Chem. Abstr.* **53**, 1750 (1959).

<sup>7</sup> W. Neugebauer, M. Tomanek, and H. Behmenburg, German Patent 1,058,836 (1959); see *Chem. Abstr.* **55**, 9129 (1961).

<sup>8</sup> A. E. Siegrist and W. Mueller (Ciba), U.S. Patent 2,856,311 (1958); see *Chem. Abstr.* **53**, 6636 (1959).

<sup>9</sup> Ciba, British Patent 816,740 (1959); see *Chem. Abstr.* **54**, 3457 (1960).

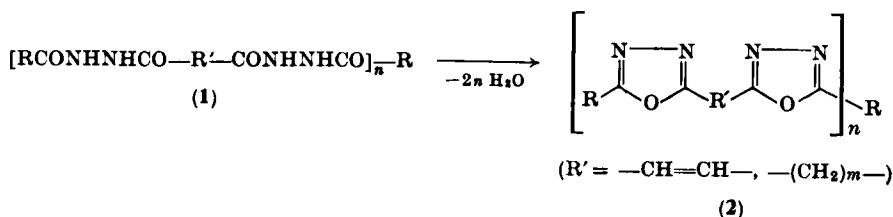
<sup>10</sup> E. Moergeli, A. E. Siegrist, and K. Hoelzle (Ciba), German Patent 1,134,782 (1962); see *Chem. Abstr.* **58**, 4675 (1963).

<sup>11</sup> E. Baltazzi and A. J. Wysocki, *Chem. Ind. (London)* p. 1080 (1963).

carried out in a "one-step process" from a monoacid hydrazide and a carboxylic acid (or ester).<sup>5-9</sup> Occasionally, in the course of a reaction using oleum, dibenzoic hydrazide derivatives are cyclized and sulfonated at the same time in the phenyl nucleus.<sup>5,9</sup> Very frequently use has been made of chlorides of phosphorus<sup>12</sup> and thionyl chloride<sup>12-19</sup> and, particularly more recently, of phosphorus oxychloride.<sup>12,18-31</sup> Diacid hydrazides may also be dehydrated by phosphoric acid and its esters.<sup>19,32-34</sup> Phosphorus pentoxide is used especially when higher temperatures are required for ring closure, e.g., in the

- <sup>12</sup> A. E. Siegrist (Ciba), German Patents 1,094,753 (1960), 1,094,754 (1959), and 1,094,755 (1960); Swiss Patent 364,790 (1962); see *Chem. Abstr.* **56**, 486 and 10161 (1962).
- <sup>13</sup> A. E. Siegrist, W. Mueller, and F. Ackermann (Ciba), Swiss Patent 347,977 (1960); see *Chem. Abstr.* **55**, 22343 (1960).
- <sup>14</sup> W. Mueller and A. E. Siegrist (Ciba), U.S. Patent 2,838,468 (1958); see *Chem. Abstr.* **53**, 1731 (1959).
- <sup>15</sup> F. Graser, German Patent 1,154,893 (1963); see *Chem. Abstr.* **60**, 6965 (1964).
- <sup>16</sup> E. Klingsberg, *J. Am. Chem. Soc.* **80**, 5786 (1958).
- <sup>17</sup> N. S. Dokunikhin, B. M. Krasovitskii, R. M. Matskevich, V. A. Blinov, and Z. Ya. Vitokhina, *Zh. Prikl. Khim.* **32**, 664 (1959); B. M. Krasovitskii, R. M. Matskevich, and N. J. Mal'tseva, *Zh. Obshch. Khim.* **31**, 2259 (1961).
- <sup>18</sup> A. Novotný, Z. Březík, J. Přidal, and K. Kalfus, *Cesk. Farm.* **7**, 517 (1958).
- <sup>19</sup> O. P. Shvaika and T. R. Mnatsakanova, *Zh. Obshch. Khim.* **34**, 2061 (1964).
- <sup>20</sup> A. P. Grekov and R. S. Azen, *Zh. Obshch. Khim.* **29**, 1995 (1959).
- <sup>21</sup> A. P. Grekov, L. N. Kulakova, and O. P. Shvaika, *Zh. Obshch. Khim.* **29**, 3054 (1959).
- <sup>22</sup> A. P. Grekov and E. P. Nesynov, *Zh. Obshch. Khim.* **30**, 3240 (1960).
- <sup>23</sup> A. P. Grekov and O. P. Shvaika, *Zh. Obshch. Khim.* **30**, 3802 (1960).
- <sup>24</sup> A. P. Grekov and R. S. Azen, *Zh. Obshch. Khim.* **31**, 407 (1961).
- <sup>25</sup> A. P. Grekov and R. S. Azen, *Zh. Obshch. Khim.* **31**, 1919 (1961).
- <sup>26</sup> A. P. Grekov and E. P. Nesynov, *Zh. Obshch. Khim.* **31**, 1122 (1961).
- <sup>27</sup> A. P. Grekov and V. I. Grigoreva, *Zh. Obshch. Khim.* **31**, 4012 (1961).
- <sup>28</sup> A. P. Grekov, *Sb. Statei, Vses. Nauchn.-Issled. Inst. Khim. Reaktivov i Osobo Chistykh Khim. Veshchestv.* No. 24, p. 131 (1961); see *Chem. Abstr.* **58**, 3418 (1963).
- <sup>29</sup> A. P. Grekov, N. P. Shimanskaya, and A. P. Kilimov, *Sb. Statei, Vses. Nauchn.-Issled. Inst. Khim. Reaktivov i Osobo Chistykh Khim. Veshchestv.* No. 24, p. 137 (1961); see *Chem. Abstr.* **58**, 5688 (1963).
- <sup>30</sup> V. N. Kerr, D. G. Ott, and F. N. Hayes, *J. Am. Chem. Soc.* **82**, 186 (1960).
- <sup>31</sup> M. D. Barnett, G. H. Daub, F. N. Hayes, and D. G. Ott, *J. Am. Chem. Soc.* **82**, 2282 (1960).
- <sup>32</sup> F. D. Popp, *J. Chem. Soc.* p. 3503 (1964).
- <sup>33</sup> T. Mukayama and T. Hata, *Bull. Chem. Soc. Japan* **34**, 99 (1961).
- <sup>34</sup> Ciba, British Patent 896,219 (1962); see *Chem. Abstr.* **58**, 12574 (1963).

preparation of bis(perfluoroalkyl)oxadiazoles.<sup>35, 36</sup> Occasionally dehydration has been effected by the use of  $\text{COCl}_2$  and  $\text{AlCl}_3$  in higher-boiling solvents, e.g., nitrobenzene.<sup>5, 9, 12</sup> The above water-abstracting substances sometimes produce low yields with heterocyclic or *o*-substituted phenyl derivatives of the hydrazides, so that these reactions are carried out at higher temperatures<sup>18, 22</sup> (180–270°) or also at reduced pressure.<sup>22</sup> The preparations of bisoxadiazoles are carried out by the above procedures<sup>11, 37</sup>; on the other hand, polyoxadiazoles (2) are formed only after several hours' heating at 120–300°



of the corresponding polyhydrazide (1) under reduced pressure,<sup>38</sup> or in the "one-step process" from dicarboxylic acid chlorides, dihydrazides, and hexamethylphosphoramide at 350°.<sup>39</sup> The degree of polymerization rises simultaneously with the formation of oxadiazole. The thermal ring closure is generally accompanied by undesirable side reactions.<sup>1, 23</sup>

2-Amino- and 2,5-diamino-1,3,4-oxadiazoles are formed by heating 1-acylsemicarbazides (3,  $\text{R} = \text{alkyl, aryl}$ )<sup>40, 41</sup> and substituted hydrazodicarboxamides (3,  $\text{R} = \text{NHR}'$ )<sup>42</sup> in an excess of phosphorus oxychloride. The yields often exceed 80%, particularly with diaryl substituents; in some cases  $\text{SOCl}_2$  may be used for the ring closure (3,  $\text{R} = \text{aralkyl}$ ,  $\text{R}' = \text{H}$ ).

<sup>35</sup> W. J. Chambers and D. D. Coffman, *J. Org. Chem.* **26**, 4410 (1961); U.S. Patent 2,992,226 (1961).

<sup>36</sup> H. C. Brown, M. T. Cheng, L. J. Parcell, and D. Pilipovich, *J. Org. Chem.* **26**, 4407 (1961).

<sup>37</sup> A. P. Grekov and M. S. Solov'eva, *Zh. Obshch. Khim.* **30**, 1644 (1960).

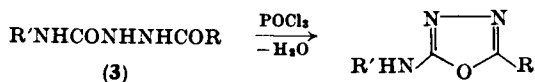
<sup>38</sup> M. Hasegawa, *J. Polymer. Sci.* **B2**, 237 (1964).

<sup>39</sup> F. T. Wallenberger, *Angew. Chem.* **76**, 484 (1964).

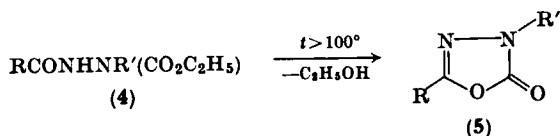
<sup>40</sup> H. Gehlen and K. Möckel, *Ann.* **660**, 144 (1962); German (East) Patent 81,370 (1963).

<sup>41</sup> A. P. Grekov, *Metody Polucheniya Khim. Reaktivov i Preparatov Gos. Kom. Sov. Min. SSSR po Khim.* No. 7, 92 (1963); see *Chem. Abstr.* **61**, 3096 (1964).

<sup>42</sup> H. Gehlen and K. Möckel, *Ann.* **685**, 176 (1965).



b. *Condensation with Elimination of Alcohol.* 1-Acylhydrazine-2-carboxylic acid esters (4) are converted on heating to 1,3,4-oxadiazolin-5-ones (5) with the elimination of alcohol.<sup>43, 43a</sup>



c. *Condensation with Elimination of Carboxylic Acids and Carboxylic Anhydrides.* Tetracylated hydrazines, which may be obtained as intermediates by heating diacyldiimides in an inert solvent or directly from anhydrous hydrazine and an excess of carboxylic acid ester, produce on heating 2,5-disubstituted 1,3,4-oxadiazoles<sup>44, 44a</sup> with the elimination of 2 moles of acid anhydride. The reaction of dibenzoyldiimide with triethyl phosphite yields, depending on the solvent, either 2,5-diphenyl-1,3,4-oxadiazole (in ether) or tribenzoic hydrazide (in chloroform).<sup>45</sup> Acylated 2-1,3,4-oxadiazolines<sup>46</sup> are formed by treating the acylhydrazones of carbonyl compounds such as benzaldehyde, acetone, and cyclohexanone with acetic anhydride or polyphosphoric acid, with the elimination of a mole of acid. In contrast to the acylation of benzoylbenzalhydrazone (6, R = R' = C<sub>6</sub>H<sub>5</sub>, R'' = H), which occasionally produces 2,5-diphenyl-1,3,4-oxadiazole, the corresponding treatment of acetone acetylhydrazone (6, R = R' = R'' = CH<sub>3</sub>) yields no 2,5-dimethyl-1,3,4-oxadiazole.<sup>46</sup>

d. *Condensation with Elimination of H<sub>2</sub>S or Mercaptans.* The known preparation of 5-substituted 2-amino-1,3,4-oxadiazoles (7) by elimination of hydrogen sulfide from 1-acylthiosemicarbazides (8)

<sup>43</sup> H. Rupe and H. Gebhardt, *Ber.* **32**, 10 (1899).

<sup>43a</sup> E. Geistlich Söhne A.G., Swiss Patent 338463 (1959).

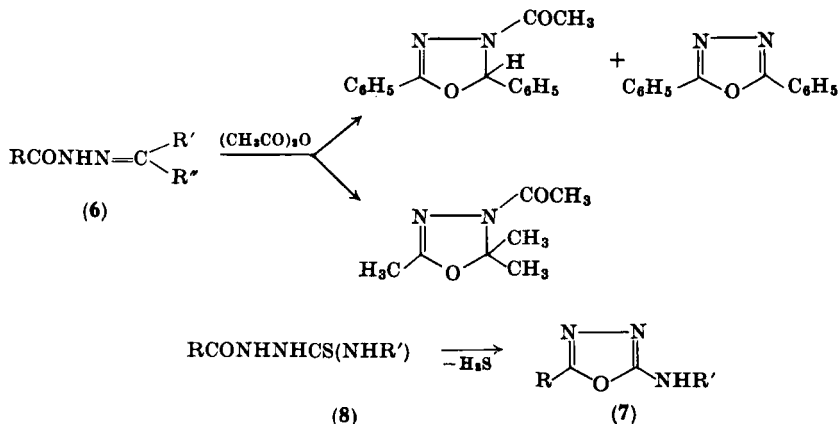
<sup>44</sup> R. Stollé and W. Reichert, *J. Prakt. Chem.* **123**, 82 (1929); *Angew. Chem.* **40**, 604 (1927); J. E. Leffler and W. B. Bond, *J. Am. Chem. Soc.* **78**, 335 (1956).

<sup>44a</sup> J. A. Young, W. S. Durrell, and R. D. Dresdner, *J. Am. Chem. Soc.* **84**, 2105 (1962).

<sup>45</sup> V. A. Ginsburg, M. N. Vasil'eva, S. S. Dubov, and A. Ya. Yakubovich, *Zh. Obshch. Khim.* **30**, 2854 (1960).

<sup>46</sup> R. S. Sagitullin and A. N. Kost, *Vestn. Moskov. Univ., Ser. Fiz. Mat. i Estestven. Nauk* **4**, 187 (1959).





using  $\text{PbO}$ <sup>47</sup> has often been modified<sup>48</sup>; thus  $\text{HgO}$ ,  $\text{Pb}_3\text{O}_4$ ,  $\text{CuSO}_4$ , and  $\text{I}_2$  may be used. The thermal cyclization of *S*-methyl ethers of the acylthiosemicarbazides follows a similar course.<sup>48, 49</sup> Because of the undesirable by-products of the above reactions as well as the yields, which are often not satisfactory, many other methods have recently been developed for the synthesis of 2-amino-1,3,4-oxadiazoles.<sup>48</sup> The syntheses of 1,3,4-oxadiazoline-5-thiones from the salts of hydrazine dithiocarboxylic acid with elimination of alkali metal hydrogen sulfide have already been fully reviewed.<sup>1</sup> Further derivatives have recently been obtained by this route.<sup>50</sup>

e. *Other Condensation Cyclizations.* 1-Cyanoformamidineacrylic acid hydrazide (9) is obtained from cyanogen and hydrazine after acylation. This compound cyclizes with the elimination of  $\text{HCN}$  after 18 hours' heating in pyridine with the addition of hydroquinone to yield 2-vinyl-5-amino-1,3,4-oxadiazole (10).<sup>51</sup>

Treatment of 1-cyanoformamidinebenzhydrazide (11) with boiling acetic acid produces 2-phenyl-1,3,4-oxadiazole-5-carboxamide (12) with elimination of  $\text{NH}_3$  and partial hydrolysis of the  $\text{CN}$  group, together with 3-cyano-5-phenyl-1,2,4-triazole (13).<sup>51</sup> The thermal

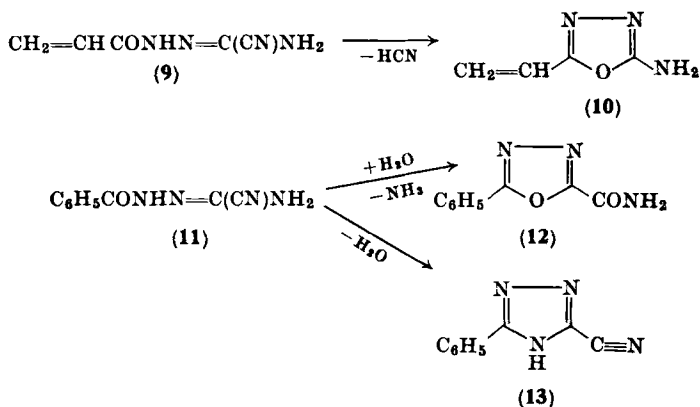
<sup>47</sup> R. Stollé and K. Fehrenbach, *J. Prakt. Chem.* **122**, 289 (1929); *Angew. Chem.* **40**, 605 (1927).

<sup>48</sup> G. Blankenstein and K. Möckel, *Z. Chem.* **2**, 69 (1962).

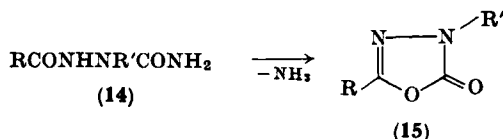
<sup>49</sup> M. Lora-Tamayo, G. Alonso, and R. Madronero, *Bull. Soc. Chim. France*, p. 259 (1964).

<sup>50</sup> O. Turilli and M. Gandino, *Ann. Chim. (Rome)* **53**, 1687 (1963).

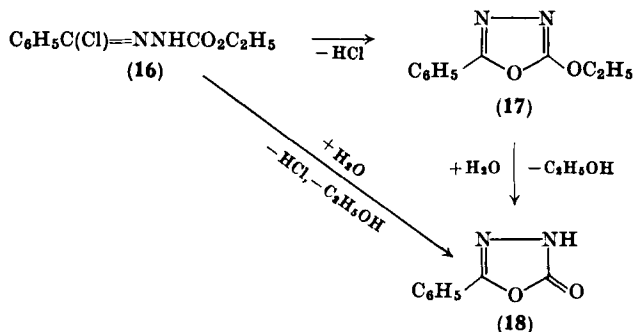
<sup>51</sup> K. Matsuda and L. T. Morin, *J. Org. Chem.* **26**, 3783 (1961).



cyclization of 1-acylsemicarbazides (14) with elimination of ammonia proceeds similarly in biphenyl<sup>52</sup> or *N*-chlorourea.<sup>53</sup> Oxadiazolinones (15) are formed in this way partly in competition with triazolinone formation. This reaction does not occur with aliphatic R groups as substituents.



$\alpha$ -Chlorobenzalcarbethoxyhydrazone (16) cyclizes with triethylamine, eliminating HCl, to give 2-phenyl-5-ethoxy-1,3,4-oxadiazole (17) (95% yield) which can be hydrolyzed to 2-phenyl-1,3,4-oxadiazolin-5-one (18). 18 is also formed together with other compounds by

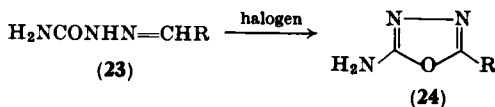


<sup>52</sup> A. Dornow and S. Lüpfer, *Arch. Pharm.* **288**, 311 (1955).

<sup>53</sup> H. Rupe and H. Labhardt, *Ber.* **33**, 233 (1900).



glacial acetic acid,<sup>59</sup> and the sodium salt of methyl *N*-chlorocarbamate.<sup>60</sup> Aldehyde semicarbazones (23) are oxidized to 2-amino-1,3,4-

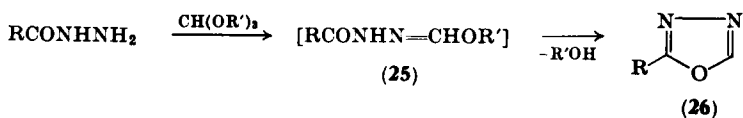


oxadiazoles (24) by bromine in aqueous alkali,<sup>59</sup> or better in glacial acetic acid<sup>59, 61-63</sup> and by iodine in aqueous sodium carbonate.<sup>64</sup> Oxidation of 1-benzal-4-methylsemicarbazone<sup>61</sup> or of 1-benzal-4,4-dimethylsemicarbazone<sup>63</sup> by bromine leads to 5-phenyl-2-methylamino- or 5-phenyl-2-dimethylamino-1,3,4-oxadiazole, respectively. According to Gibson,<sup>62</sup> the oxidative cyclization of hydrazones and semicarbazones involves an intramolecular 1,3-dipolar addition, which contrasts with the apparently radical mechanism for the formation of triazolinones from semicarbazones with  $\text{FeCl}_3$ .

## B. SYNTHESSES FROM ACID HYDRAZIDES BY THE INTRODUCTION OF A ONE-CARBON FRAGMENT

### 1. *Syntheses from Acid Hydrazides and ortho Esters*

The reaction of acid hydrazides with orthoformic esters proceeds via 25<sup>65, 66</sup> with elimination of alcohol to give 2-substituted 1,3,4-oxadiazoles (26). The reaction is mostly carried out with the reactants at the boiling point of the orthoformic ester or in an inert solvent at



<sup>60</sup> C. P. de la Saulinière, *Ann. Chim. (Paris)* [11] **17**, 353 (1942).

<sup>61</sup> G. Werber and F. Maggio, *Ann. Chim. (Rome)* **52**, 747 (1962).

<sup>62</sup> M. S. Gibson, *Tetrahedron* **18**, 1377 (1962).

<sup>63</sup> H. Najer, J. Menin, and J. F. Guidicelli, *Compt. Rend.* **258**, 4579 (1964).

<sup>64</sup> H. Gehlen and K. Möckel, *Ann.* **651**, 133 (1962).

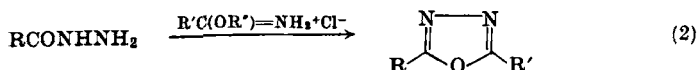
<sup>65</sup> C. Ainsworth, *J. Am. Chem. Soc.* **77**, 1148 (1955); **78**, 1636 (1956); **87**, 5800 (1965); U.S. Patents 2,702,803 (1955) and 2,733,245 (1956).

<sup>66</sup> M. Itoh, *Yakugaku Kenkyu* **34**, 410 (1962).

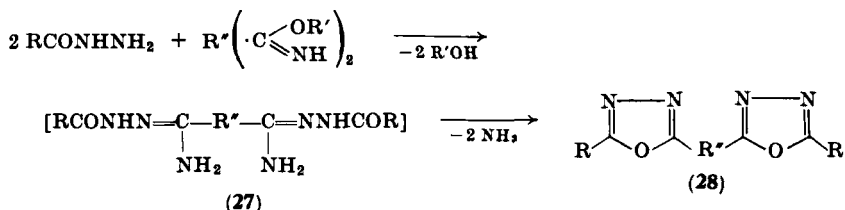
a higher temperature.<sup>37, 65-70a</sup> Thus the acid hydrazides can be cyclized only when R is sufficiently electrophilic; an aromatic group, however, is not necessary.<sup>69</sup>

## 2. Syntheses from Acid Hydrazides and Imido Esters or Imidochlorides

A universal method for the preparation of 2,5-dialkyl(aryl)-1,3,4-oxadiazoles is the reaction of acid hydrazides with imido esters or their hydrochlorides [Eq. (2)].<sup>1, 2, 71-74</sup>



Bisoxadiazoles are formed from bis(mono)imido ester hydrochlorides and mono(bis)carboxylic acid hydrazides; when the free ester is used, an amidrazone (27) is often formed which cyclizes with the elimination of ammonia to give 28.<sup>73</sup> The reaction proceeds in the presence of higher boiling solvents or by mixing the reactants at a temperature higher than 100°, the imido esters forming first in the reaction mixture. The reaction of semicarbazide [Eq. (2), R = NH<sub>2</sub>] with imido esters does not, of course, lead to 2-amino-1,3,4-oxadiazoles but to the isomeric 1,2,4-triazolin-3-ones.<sup>72</sup> The reaction of *N*-substituted imidochlorides with aromatic acid hydrazides in the



<sup>67</sup> A. P. Grekov, O. P. Shvaika, and L. M. Egupova, *Zh. Obshch. Khim.* **29**, 2027 (1959).

<sup>68</sup> J. Maillard, M. Vincent, and M. Benard, *Bull. Soc. Chim. France* p. 529 (1961).

<sup>69</sup> M. Vincent, J. Maillard, and M. Benard, *Bull. Soc. Chim. France* p. 1580 (1962).

<sup>70</sup> Soc. d'Exploitation des Laboratoires J. Logeais, French Patent M-1,324 (1962); see *Chem. Abstr.* **58**, 1468 (1963).

<sup>70a</sup> A. A. Ponomarev and Z. V. Til, *Zh. Obshch. Khim.* **33**, 2368 (1963).

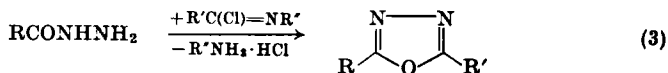
<sup>71</sup> H. Weidinger and J. Kranz (BASF), French Patent 1,222,050 (1959); see *Chem. Zentr.* p. 8064 (1962); German Patent 1,067,439 (1958); see *Chem. Abstr.* **56**, 3485 (1962).

<sup>72</sup> J. Kranz and H. Weidinger, *Festschr. Karl Wurster* p. 119 (1960).

<sup>73</sup> H. Weidinger and J. Kranz, *Ber.* **96**, 1049 (1963).

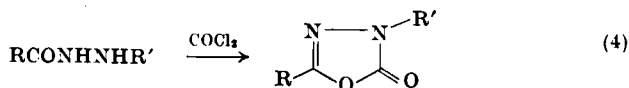
<sup>74</sup> M. Pesson, S. Dupin, and M. Antoine, *Bull. Soc. Chim. France* p. 1364 (1962).

presence of basic solvents produces 2,5-disubstituted 1,3,4-oxadiazoles with the elimination of amine hydrochloride [Eq. (3)].<sup>75</sup>



### 3. Syntheses from Acid Hydrazides with Phosgene, Thiophosgene, Carbon Disulfide, or Isocyanide Dichlorides

Acid hydrazides with phosgene produce 1,3,4-oxadiazolin-5-ones [Eq. (4)]. Particular attention has been devoted recently to hetero-



cyclic substituents and also to certain aromatic derivatives (cf. Section V).<sup>18, 76-87b</sup> For example, 2-(2-nitro-5-furyl)-1,3,4-oxadiazolin-5-one,<sup>77, 78, 81</sup> several alkylated 2-isoxazolyl-1,3,4-oxadiazolin-5-ones,<sup>82, 83</sup> 2-pyrazinyl-1,3,4-oxadiazolin-5-one,<sup>84</sup> and derivatives of

<sup>75</sup> H. Weidinger and H. Eilingsfeld, German Patent 1,113,053 (1961).

<sup>76</sup> H. C. Caldwell, R. J. Seiwald, and J. H. Burckhalter, *J. Am. Pharm. Assoc., Sci. Ed.* **47**, 799 (1958).

<sup>77</sup> W. R. Sherman, U.S. Patent 2,918,473 (1959).

<sup>78</sup> W. R. Sherman, *J. Org. Chem.* **26**, 88 (1961).

<sup>79</sup> H. Inoue and A. Saikachi, Japanese Patent 20,572 (1963); see *Chem. Abstr.* **60**, 2952 (1964).

<sup>80</sup> M. Meislová and V. Nedvedová, *Rozhledy Tuberk.* **18**, 724 (1958).

<sup>81</sup> H. Saikachi, British Patent 949,288 (1964); see *Chem. Abstr.* **60**, 10692 (1964).

<sup>82</sup> T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.* **26**, 1514 (1961).

<sup>83</sup> S. V. Sokolov and I. J. Postovskii, *Zh. Obshch. Khim.* **30**, 1781 (1960).

<sup>84</sup> A. E. Wilder-Smith and E. Frommel, *Arzneimittel-Forsch.* **12**, 485 (1962).

<sup>85</sup> A. E. Wilder-Smith, *Arzneimittel-Forsch.* **12**, 22, 275 (1962).

<sup>86</sup> A. E. Wilder-Smith, *Arch. Pharm.* **295**, 455 (1962).

<sup>87</sup> A. E. Wilder-Smith, Hungarian Patent 150,568 (1963); see *Chem. Zentr.* **32**, 182/1543 (1964); U.S. Patent 3,127,410 (1964); see *Chem. Abstr.* **61**, 3118 (1964).

<sup>87a</sup> E. Jucker and A. Lindenmann, *Helv. Chim. Acta* **45**, 2316 (1962).

<sup>87b</sup> J. Hadáček and J. K. Opavský, *Spisy Vydavane Prirodovedeckou Fak. Masary. Univ.* **8**, No. 373, 147 (1956).

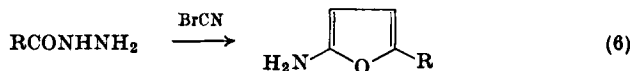
isonicotinic acid hydrazide<sup>18, 76, 80, 84-87</sup> and of *p*-aminosalicylic acid hydrazide<sup>84-87</sup> have been described. The corresponding 1,3,4-oxadiazoline-5-thiones are also known, these compounds being prepared analogously from the acid hydrazides with thiophosgene or preferably carbon disulfide.<sup>77, 78, 83, 88-91</sup>

Acid hydrazides and 4-arylsemincarbazides [Eq. (5), R = NHAr] cyclize on heating for a short time with an excess of phenylisocyanide-dichloride to give 2-amino-1,3,4-oxadiazoles [Eq. (5)].<sup>92</sup>



#### 4. Syntheses from Acid Hydrazides with Bromine Cyanide

Acid hydrazides are cyclized by bromine cyanide in aqueous bicarbonate or other solvents to form 5-substituted 2-amino-1,3,4-oxadiazoles [Eq. (6)].<sup>48, 78, 93, 94</sup> The yields here are almost without



exception higher than those in the procedures described in Section II, A. According to Sherman,<sup>78</sup> for example, 2-amino-5-(2-nitro-5-furyl)-1,3,4-oxadiazole is formed in 64% yield in contrast to the 16% from 1-(2-nitro-5-furoyl)thiosemicarbazide and  $\text{Pb}_3\text{O}_4$ . Futaki<sup>95</sup> obtained in 28% yield 2-amino-5-phenyl-1,3,4-oxadiazole by treating 2-methane-sulfonyl-5-phenyl-1,3,4-oxadiazole with ammonia, while

<sup>88</sup> W. Siefken and H. B. König, German Patent 950,639 (1956).

<sup>89</sup> J. Hadáček and J. Trgala, *Spisy Prirodovedcke Fak. Univ. Brne* p. 7 (1959); see *Chem. Abstr.* **55**, 2895 (1961).

<sup>90</sup> A. L. Mndzhoyan, G. T. Tatevosyan, S. G. Agbalyan, and N. M. Divanyan, *Dokl. Akad. Nauk Arm. SSR* **25**, 207 (1957).

<sup>91</sup> A. L. Mndzhoyan, G. T. Tatevosyan, A. G. Tercyan, and S. P. Ekmekdzhyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauk* **11**, 127 (1958).

<sup>92</sup> K. Möckel and H. Gehlen, *Z. Chem.* **10**, 388 (1964).

<sup>93</sup> H. Gehlen, *Ann.* **563**, 185 (1949); H. Gehlen and G. Blankenstein, *ibid.* **638**, 136 (1960).

<sup>94</sup> A. P. Swain, U.S. Patent 2,883,391 (1959); see *Chem. Abstr.* **53**, 16157 (1959).

<sup>95</sup> K. Futaki and S. Tosa, *Chem. Pharm. Bull. (Tokyo)* **8**, 908 (1960).

benzoic hydrazide and bromine cyanide react to form 2-amino-5-phenyl-1,3,4-oxadiazole quantitatively.<sup>93</sup> The reaction can also be carried out in a "one-step process" using potassium cyanide, bromine, and the acid hydrazide in aqueous bicarbonate solution.<sup>96</sup> In the reaction 1,2,4-triazolin-5-ones are generally formed as by-products and in alkaline media 3-substituted 5-alkoxy-1,2,4-triazoles are also formed. By modifying the reaction conditions either compound may be formed as the main product.<sup>97</sup>

2-Arylamino-5-amino-1,3,4-oxadiazoles are formed from 4-arylsemicarbazides with bromine cyanide [Eq. (7)],<sup>98</sup> but 1,4-diphenyl-3-

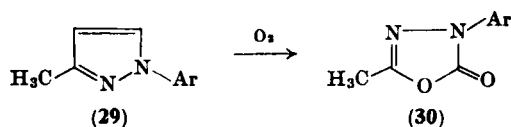


amino-1,2,4-triazolin-5-one is formed from 2,4-diphenylsemicarbazide, apparently because of the very low stability of the expected oxadiazole derivative.<sup>99</sup>

### C. PREPARATION FROM OTHER RING SYSTEMS

#### 1. Rearrangement of Pyrazoles and Hydantoins to 1,3,4-Oxadiazoles

2-Methyl-4-aryl-1,3,4-oxadiazolin-5-one (30) is obtained by the



action of ozone on 1-aryl-3-methylpyrazole (15).<sup>100</sup> 2-Substituted hydantoins [Eq. (8)] are rearranged in a well-known manner<sup>1</sup> in the

<sup>96</sup> I. Čipen and V. J. Grinstejn, *Izv. Akad. Nauk Latv. SSR, Ser. Khim.* **2**, 255 (1962).

<sup>97</sup> H. Gehlen and M. Just, German (East) Patent 85,652 (1964).

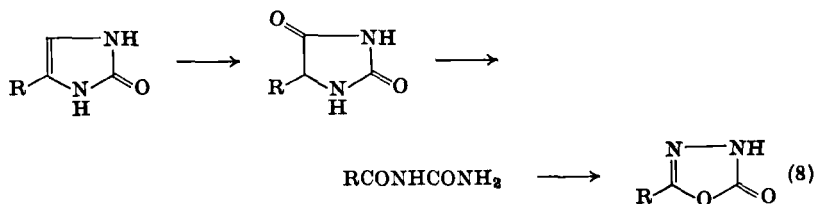
<sup>98</sup> H. Gehlen and W. Schade, *Ann.* **675**, 176 (1964).

<sup>99</sup> H. Gehlen and G. Blankenstein, *Ann.* **627**, 162 (1959).

<sup>100</sup> J. P. Wibaut and J. W. P. Boon, *Helv. Chim. Acta* **44**, 1171 (1961).

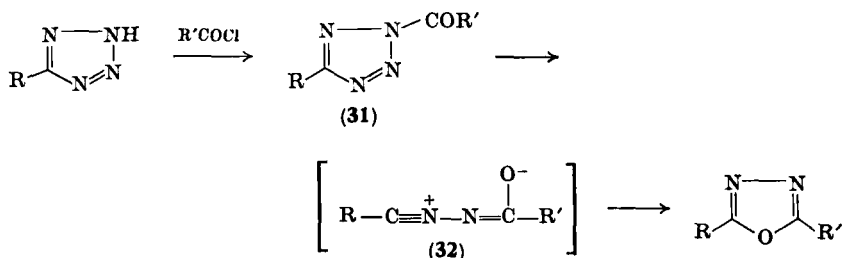


presence of hypobromite to give 2-substituted 1,3,4-oxadiazolin-5-ones.<sup>100a</sup>



## 2. Preparation by Ring Cleavage of Tetrazoles

The rearrangement of 1-aryl-5-aminotetrazoles by the action of acetic anhydride to 2-arylamino-5-methyl-1,3,4-oxadiazoles or to their acetyl derivatives has been known for some time.<sup>101, 102</sup> This reaction may be widely generalized. The action of aromatic and aliphatic acid anhydrides and acid chlorides on 5-alkyl(aryl)tetrazoles produces 1,3,4-oxadiazoles in excellent yield. *N*-Acyltetrazoles (31) are formed as intermediates. These are converted with elimination of



nitrogen into the hypothetical *N*-acylnitrilimines (32) which are immediately stabilized as the 1,3,4-oxadiazoles.<sup>103</sup>

This mechanism was demonstrated in the following manner. The N atoms 1 and 4 in 5-phenyltetrazole were labeled with <sup>15</sup>N. Half of

<sup>100a</sup> V. M. Rodionov and V. V. Kiseleva, *Izv. Akad. Nauk. SSSR Otd. Khim. Nauk*, p. 608 (1950); p. 57 (1951); p. 513 (1953); S. I. Kanevskaya and D. S. Yaskina, *Zh. Obshch. Khim.* **27**, 68 (1957).

<sup>101</sup> R. Stollé, *Ber.* **62**, 1118 (1929).

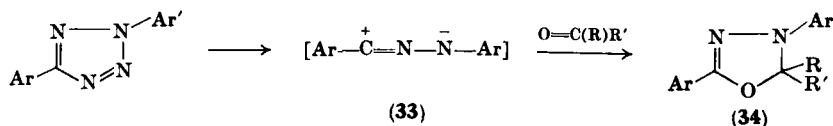
<sup>102</sup> R. M. Herbst and J. E. Klingbeil, *J. Org. Chem.* **23**, 1912 (1958).

<sup>103</sup> R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.* **70**, 272 (1958); R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Ber.* **93**, 2106 (1960); J. Sauer, R. Huisgen, and H. J. Sturm, *Tetrahedron* **11**, 241 (1960).

the  $^{15}\text{N}$  was found in the 2,5-diphenyl-1,3,4-oxadiazole which was obtained by the breakdown of the 5-phenyltetrazole with benzoyl chloride. Therefore either the N atoms 1 and 2 or 3 and 4 were eliminated as  $\text{N}_2$ .<sup>104</sup>

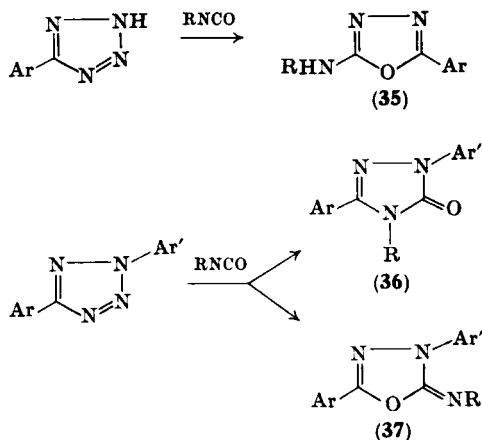
Polymeric 1,3,4-oxadiazoles can be prepared by the action of diacid chlorides on bistetrazoles.<sup>105</sup> The products, obtained after several days' heating of the reactants in pyridine, have a low degree of polymerization but high thermal stability.

Intermediate *C,N*-disubstituted nitrilimines (33) are obtained by



thermolysis of 2,5-diaryltetrazoles or by HCl elimination from acid hydrazide halides.<sup>106, 107</sup> These 1,3-dipoles may undergo cycloaddition reactions. Thus  $\Delta^2$ -1,3,4-oxadiazolines (34) are obtained using aromatic aldehydes or activated ketones.

The reaction of tetrazoles with isocyanates at elevated temperatures



<sup>104</sup> R. M. Herbst, *J. Org. Chem.* **26**, 2372 (1961).

<sup>105</sup> C. J. Abshire and C. S. Marvel, *Makromol. Chem.* **44-46**, 388 (1961).

<sup>106</sup> R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland, and G. Wallbillich, *J. Org. Chem.* **24**, 892 (1959).

<sup>107</sup> R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, and R. Schmidt, *Ann.* **658**, 169 (1962).

also proceeds by a 1,3-dipolar addition to the intermediate nitrilimine.<sup>108, 109</sup> The action of heat on 5-aryltetrazoles in the presence of arylisocyanates leads to 2-arylamino-5-aryl-1,3,4-oxadiazoles (35). If one uses 2,5-diaryltetrazoles, then 1,3,4-triaryl-1,2,4-triazolin-5-ones (36) and 2,4-diaryl-5-arylamino-1,3,4-oxadiazolines (37) are isolated. The relative yields depend on the substituents.

### 3. Rearrangement of Tetrazines to 1,3,4-Oxadiazoles

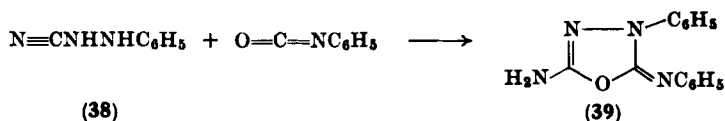
A mechanism similar to the one described for the formation of 1,3,4-oxadiazolines from tetrazoles and carbonyl compounds is postulated also for the reaction of hexahydrotetrazine derivatives in the 3,4-dihydroisoquinoline series with carbonyl compounds.

Azomethinimine derivatives (92) are formed as intermediates, and 1,3,4-oxadiazolidines (91) are isolated as the end products of the reaction<sup>110</sup> (cf. Section III, B, 4).

3,6-Diphenyl-1,2,4,5-tetrazine on heating with hydrochloric acid yields 2,5-diphenyl-1,3,4-oxadiazole together with dihydrotetrazine.<sup>111</sup> This long-established reaction when carried out in the presence of peracetic acid and sodium acetate at 50–60° leads almost exclusively to the oxadiazole.<sup>112</sup>

## D. OTHER SYNTHESSES

The ring closure of *N*-cyano-*N*-phenylhydrazines with either phenylisocyanate or acid chlorides leads to 2-amino-1,3,4-oxadiazoles or 2-imino-1,3,4-oxadiazolines, respectively. Thus 2,4-diphenyl-5-imino-1,3,4-oxadiazoline is formed from *N*-cyano-*N*-phenylhydrazine and benzoyl chloride,<sup>113</sup> while *N*'-cyano-*N*-phenylhydrazine (38)



<sup>108</sup> R. Huisgen, H. J. Sturm, and M. Seidel, *Ber.* **94**, 1555 (1961).

<sup>109</sup> R. Huisgen, R. Grashey, H. Knupfer, R. Kunz, and M. Seidel, *Ber.* **97**, 1085 (1964).

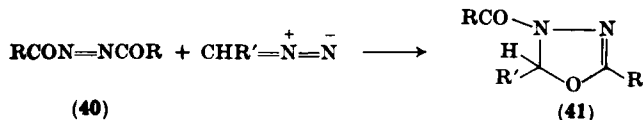
<sup>110</sup> R. Grashey and K. Adelsberger, *Angew. Chem.* **74**, 292 (1962).

<sup>111</sup> A. Pinner and N. Caro, *Ber.* **27**, 3273 (1894).

<sup>112</sup> J. Allegretti, J. Hancock, and R. S. Knutson, *J. Org. Chem.* **27**, 1463 (1962).

<sup>113</sup> G. Pellizzari, *Gazz. Chim. Ital.* **56**, 695 (1926).

reacts with phenyl isocyanate in the cold to yield 2-amino-4-phenyl-5-phenylimino-1,3,4-oxadiazoline (39).<sup>99</sup> 2,2-Diphenyl-5-diphenylmethylene-1,3,4-oxadiazoline (86) is obtained by the addition of diphenylketene to diphenyldiazomethane<sup>114</sup> (see Section III, B, 4). Dibenzoyldiimide (40, R = C<sub>6</sub>H<sub>5</sub>) and azodicarboxylic ester (40, R = OC<sub>2</sub>H<sub>5</sub>)

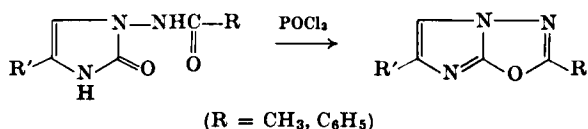


similarly add aliphatic diazo compounds with the formation of 1,3,4-oxadiazolines (41, R = C<sub>6</sub>H<sub>5</sub>, OC<sub>2</sub>H<sub>5</sub>).<sup>115</sup> The structure of 41 was demonstrated by UV and NMR spectroscopy.

The preparation of particular 1,3,4-oxadiazole derivatives by substitution of functional groups will be dealt with in Section III, A.

### E. CONDENSED 1,3,4-OXADIAZOLES

Previously only a few condensed 1,3,4-oxadiazoles were known. Pyrido[2,1-*b*]1,3,4-oxadiazol-2-one and the quinoline analog are obtained by the action of phosgene on 1-aminopyrid-2-one and 1-aminoquinol-2-one, respectively.<sup>116</sup> These compounds display a mesoionic character. Furthermore, imidazolo[2,1-*b*]1,3,4-oxadiazoles



SCHEME I

have been prepared from 1-acetamido- and 1-benzamidoimidazolin-2-one (cf. Scheme I).<sup>117</sup> 7-Oxo-5-hydroxy-7*H*-1,3,4-oxadiazolo[3,2-*a*]pyrimidine has been obtained from 2-amino-1,3,4-oxadiazole and carbon suboxide.<sup>118</sup>

<sup>114</sup> W. Kirmse, *Ber.* **93**, 2357 (1960).

<sup>115</sup> R. Breslow, C. Yaroslavsky, and S. Yaroslavsky, *Chem. Ind. (London)*, p. 1961 (1961).

<sup>116</sup> K. Hoergerle, *Helv. Chim. Acta* **41**, 548 (1958).

<sup>117</sup> H. Beyer and A. Hetzheim, *Z. Chem.* **2**, 153 (1962).

<sup>118</sup> E. Ziegler and R. Wolf, *Monatsh.* **93**, 1441 (1962).

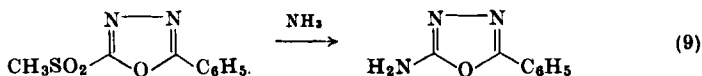
### III. Reactivity of the 1,3,4-Oxadiazoles

#### A. SUBSTITUTION REACTIONS AND STRUCTURE OF 1,3,4-OXADIAZOLES

##### 1. Direct Ring Substitutions

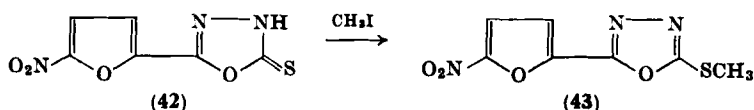
The direct introduction of functional groups into the oxadiazole nucleus is possible in only a few cases. The protonation of the nuclear nitrogen in acidic media reduces extremely strongly the possibility of electrophilic attack.<sup>119</sup> Thus no nitrations or sulfonations of unsubstituted oxadiazoles are known in the literature. Halogenation also has not so far been described although in this case the deactivating effect of the oxadiazole nucleus is not so important.<sup>47, 61</sup>

The introduction of other functional groups into the oxadiazole nucleus by nucleophilic substitution of substituted 1,3,4-oxadiazoles is also difficult (cf. Section III, B). The few known examples proceed with low yield.<sup>1</sup> Thus 2-phenyl-5-amino-1,3,4-oxadiazole is obtained by ammonolysis of 2-phenyl-5-methanesulfonyl-1,3,4-oxadiazole [Eq. (9)].<sup>95</sup>



##### 2. Alkylation and Acylation

1,3,4-Oxadiazoline-5-thione, 1,3,4-oxadiazolin-5-one, 2-amino-1,3,4-oxadiazole, and 2-benzyl-5-aryl-1,3,4-oxadiazole may be alkylated and acylated. As a result of the mesomerism of these compounds the ring nitrogen can also be substituted. Alkylation has been carried out on many 1,3,4-oxadiazoline-5-thiones.<sup>1, 120</sup> (They also react with other active halogen compounds such as perchloromethylmercaptan<sup>121</sup> and 2,4-dinitrochlorobenzene.<sup>50</sup>) Thus 2-(2-nitro-5-furyl)1,3,4-oxadiazoline-5-thione (42) is methylated by the action of methyl iodide



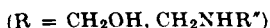
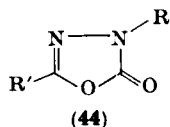
<sup>119</sup> A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," p. 220. Methuen, London (Wiley, New York), 1960.

<sup>120</sup> M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **33**, 1394 (1960).

<sup>121</sup> J. Metivier and R. Boesch, French Patent 1,337,286 (1963); see *Chem. Abstr.* **60**, 4157 (1964).

in the presence of ethanolic potassium hydroxide. Since the absorption in the IR spectrum at  $7.57$  and  $7.65 \mu$  is greatly reduced and moreover no  $\text{N}-\text{CH}_3$  band appears, the compound 2-(2-nitro-5-furyl)-5-methylthio-1,3,4-oxadiazole (43) is probably present.<sup>78</sup>

1,3,4-Oxadiazolin-5-ones which, according to the IR spectra, exist in the oxo form, at least in the solid state (cf. Section IV), may be alkylated at the ring nitrogen by means of the Mannich reaction.<sup>52, 76</sup> 4-Hydroxymethyl- and 4-dialkylaminomethyl-1,3,4-oxadiazolin-5-ones (44) are formed using formaldehyde or formaldehyde with a

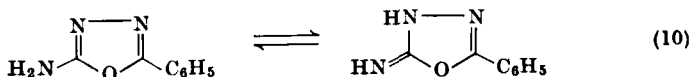


secondary amine, respectively. In the presence of mineral acids, rapid and quantitative reformation of the oxadiazolinone occurs.<sup>78</sup> Particular interest has lately been directed to the alkylation and acetylation reactions of the 2-amino-1,3,4-oxadiazoles in connection with the investigation of their tautomeric relationships (cf. Section IV).

Alkylation of 2-amino-1,3,4-oxadiazoles in neutral medium, according to previous observations, always occurs primarily at the ring nitrogen.<sup>122</sup>

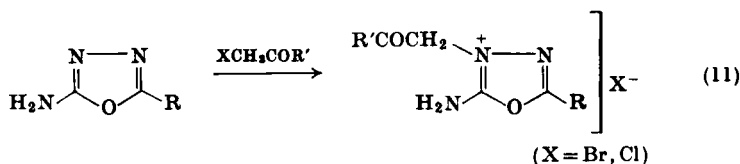
Thus, 2-imino-3-methyl-5-phenyl-1,3,4-oxadiazoline is obtained from the methylation of 2-amino-5-phenyl-1,3,4-oxadiazole with methyl iodide.<sup>61, 63</sup> Only in a sealed tube with an excess of methyl iodide is 2-methylimino-3-methyl-5-phenyl-1,3,4-oxadiazoline formed.<sup>63</sup> The structure of the alkylated product was confirmed by its nonidentity with 2-methylamino-5-phenyl-1,3,4-oxadiazole or 2-dimethylamino-5-phenyl-1,3,4-oxadiazole which were synthesized by an independent route.

It was established by comparison of the UV, fluorescence, and IR spectra and the  $\text{p}K_a$  values of the above alkylated products that 2-amino-5-phenyl-1,3,4-oxadiazole predominates in the tautomeric equilibrium [Eq. (10)].<sup>63</sup> Alkylation of 2-amino-5-methyl(phenyl)-1,3,4-oxadiazoles with aromatic  $\alpha$ -haloketones also takes place at



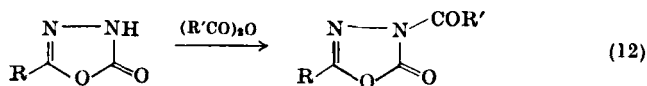
<sup>122</sup> J. Goerdeler and W. Roth, *Angew. Chem.* **70**, 400 (1958).

the ring nitrogen<sup>123</sup>; 2-amino-3-phenacyl-5-methyl(phenyl)-1,3,4-oxadiazolium halide is obtained (cf. Section III, B) [Eq. (11)]. On the

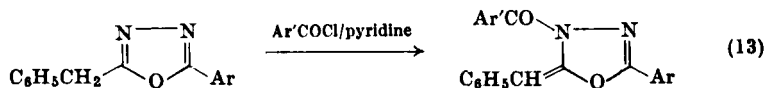


other hand, in the alkylation of 2-acetamido-5-phenyl-1,3,4-oxadiazole with methyl iodide in the presence of sodium *tert*-butoxide or with dimethyl sulfate in alkaline solution, the amino group is substituted, and 2-methylacetamido-5-phenyl-1,3,4-oxadiazole is formed.<sup>61</sup>

Acylation of 2-amino-1,3,4-oxadiazoles produces 2-acylamino-1,3,4-oxadiazoles.<sup>1, 63, 124, 125</sup> A series of acylamino derivatives, mainly 2-arylsulfonylamido-1,3,4-oxadiazoles, has been prepared.<sup>48</sup> As has been mentioned, the 1,3,4-oxadiazolin-5-ones exist in the oxo form at least in the solid state. Acetylation proceeds with substitution of the ring nitrogen [Eq. (12)]. The possibility of *O*-acetylation



is ruled out by the IR spectrum since the acetyl compound shows two C=O absorptions, at 5.50 and 5.70  $\mu$ . Similarly, 2-benzyl-5-aryl-1,3,4-oxadiazole, because of its active methylene group, is acylated by aromatic acid chlorides in pyridine to give 2-benzylidene-3-aroyle-5-aryl-1,3,4-oxadiazoline (yield 15%) [Eq. (13)].<sup>103</sup>



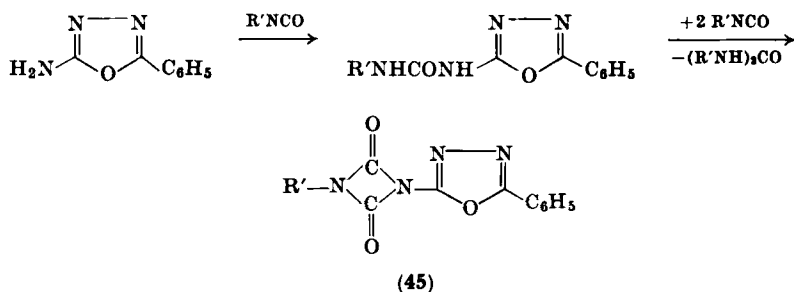
<sup>123</sup> H. Beyer and A. Hetzheim, *Z. Chem.* **2**, 152 (1962).

<sup>124</sup> N. A. Joensson, Swedish Patent 174, 465 (1957); see *Chem. Abstr.* **56**, 7331 (1962); B. Hökfelt and A. Joensson, *J. Med. Pharm. Chem.* **5**, 247 (1962); see *Chem. Abstr.* **57**, 3568 (1962).

<sup>125</sup> Aktiebolaget Astra Apotekarnes Kemiska Fabriker, Swedish Patent 826,539 (1960); British Patent 826,539 (1960); see *Chem. Abstr.* **54**, 9960 (1960).

## 3. Other Reactions of 2,5-Disubstituted 1,3,4-Oxadiazoles

In addition to a series of previously well-known reactions of 2-amino-1,3,4-oxadiazoles such as the formation of Schiff's bases or phthalamido derivatives,<sup>48, 59, 61, 93</sup> it has been possible to convert 2-amino-5-phenyl-1,3,4-oxadiazole by addition of isocyanate via the corresponding urea into (5-phenyl-1,3,4-oxadiazol-2-yl)diazetidinediones (45).<sup>126</sup>



Derivatives of the 2-phenyl-1,3,4-oxadiazole-5-carboxylic acids give the usual reactions of acids on careful treatment.<sup>103</sup> Thus the alcoholysis of the 5-acid chlorides with methanol or ethanol leads to the corresponding ester. Alkaline hydrolysis at 30° produces the carboxylic acid which on warming is decarboxylated to 2-phenyl-1,3,4-oxadiazole. Even a slight increase in the severity of the reaction conditions produces ring cleavage.<sup>103</sup> The alkaline hydrolysis of 2-phenyl-5-(*p*-cyanophenyl)-1,3,4-oxadiazole with addition of H<sub>2</sub>O<sub>2</sub> leads to 2-phenyl-5-(*p*-carboxamidophenyl)-1,3,4-oxadiazole.<sup>23</sup>

2,5-Diaryl-1,3,4-oxadiazoles and their derivatives exhibit the known substitution reactions at the aryl residue. Oleum leads to the sulfonic acid derivatives<sup>9, 14</sup> and nitric acid and sulfuric acid lead to the nitroaryl compounds.<sup>25</sup> From these nitro compounds the corresponding aminophenyl-1,3,4-oxadiazoles may be prepared in good yield using reducing agents such as iron and hydrochloric acid,<sup>6</sup> sodium hydrogen sulfide,<sup>17</sup> or phenylhydrazine.<sup>21, 23</sup> Diazonium salts are obtained with nitrous acid and these show the usual reactions. The diazonium salts are starting materials for textile dyestuffs (cf. Section V). 2-Aryl-1,3,4-oxadiazoles are often sensitive even in the cold to acid and alkaline media (cf. Section III, B, 1). Their nitroaryl derivatives can therefore only be prepared by means of a direct synthesis of the

<sup>126</sup> H. Gehlen and M. Just, *Ann.* **692**, 151 (1966).



1,3,4-oxadiazole ring. Reduction to the amine is carried out with phenylhydrazine<sup>67</sup> or hydrogen in the presence of palladium.<sup>68</sup>

Etherification or esterification of hydroxyphenyl-1,3,4-oxadiazole is possible in good yield.<sup>21, 70</sup> The same is true for acetylation of the aminophenyl derivatives.<sup>21, 70</sup>

## B. REACTIONS PROCEEDING WITH RING CLEAVAGE

In contrast to its high thermal stability the 1,3,4-oxadiazole ring proves extremely labile to chemical agents. Ring cleavage reactions of 1,3,4-oxadiazoles can be achieved by the action of reducing agents and by nucleophilic reagents; in special cases the ring opening is possible either by thermolysis or photolysis. Although in reduction cleavage of the N—N bond takes place with amide formation, in an attack by a nucleophilic reagent the C—O bond of the 1,3,4-oxadiazole is opened. Of the two ring-opening reactions the latter makes up a relatively greater portion of the more recent work.

The ring-opening tendency, assuming equal solubility in the reaction medium concerned, is controlled in general by the electron density at the C-2 or C-5 atom, which is largely dependent on the substituents, and by the nucleophilicity of the reactants. Ethanol, water, aqueous carbonate solution, ethoxide, ethanolic and aqueous hydroxide, ammonia, amines, hydrazines, hydrazides, hydrogen sulfide, and mineral acids have all been used as nucleophilic reagents.

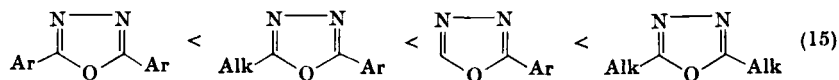
### 1. *Ring Cleavage of Alkyl-, Aryl-, and Heterocyclic-Substituted 1,3,4-Oxadiazoles*

Ring cleavage of the 2,5-dialkyl-1,3,4-oxadiazoles by either acid or base leading to carboxylic acids and hydrazine or acid hydrazides [Eq. (14)] has been known for some time.<sup>1</sup> Investigation of the



acid hydrolysis of alkyl- and aryl-substituted 1,3,4-oxadiazoles and its dependence on the substituents has recently been reinvestigated.<sup>24, 26</sup> In general, the aryl-substituted 1,3,4-oxadiazoles are less sensitive to acid than the alkyl-substituted derivatives. Grekov

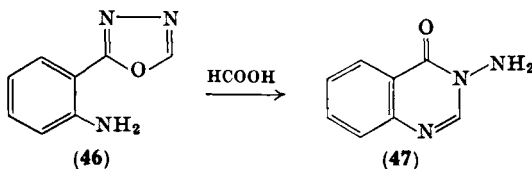
*et al.* have established that the susceptibility to hydrolysis increases with increasing solubility in the series shown in Eq. (15).<sup>24</sup>



No hydrolysis is observed when 2,5-diphenyl-1,3,4-oxadiazole, which has a solubility in water of 0.03%, is treated with mineral acids. Neither concentrated  $\text{HNO}_3$  nor treatment with fuming  $\text{H}_2\text{SO}_4$  at  $100^\circ$  for 4 hours attacks the oxadiazole ring. Similar stability is shown by 2-( $\omega$ -styryl)-5-aryl-1,3,4-oxadiazole.<sup>19</sup> On the other hand, the attempt to obtain the free acid by treatment of 2-phenyl-5-*p*-carboxyphenyl-1,3,4-oxadiazole with caustic soda produces 1-*p*-carboxybenzoyl-2-benzoylhydrazine.<sup>23</sup> Other aryl-substituted compounds as well as 1,3,4-oxadiazoles substituted in the 2,5-position by various heterocyclic groups are hydrolyzed by mineral acids.<sup>26</sup>

The majority of 2-alkyl-5-aryl-1,3,4-oxadiazoles can easily be cleaved in mineral acid solution to give the corresponding diacid hydrazides. 2-( $\alpha$ -Bromoethyl)-5-phenyl-1,3,4-oxadiazole is hydrolyzed so easily that even during the synthesis from 1- $\alpha$ -bromopropionyl-2-benzoylhydrazine, on treating the reaction mixture with water, partial hydrolysis occurs to give the diacid hydrazide or even hydrazine.<sup>19</sup> This can be eliminated in the synthesis by among other means the use of petrol ether in place of water. The 2-bromomethyl-5-aryl-1,3,4-oxadiazoles are extremely stable.<sup>19</sup>

Most of the freely soluble 2-aryl-1,3,4-oxadiazoles can be hydrolyzed in acid or alkaline solution even more readily than the 2-alkyl-5-aryl-1,3,4-oxadiazoles. This also applies to the 2-aryl-1,3,4-oxadiazoles which are substituted in the aryl nucleus.<sup>67, 127</sup> In the hydrolysis of



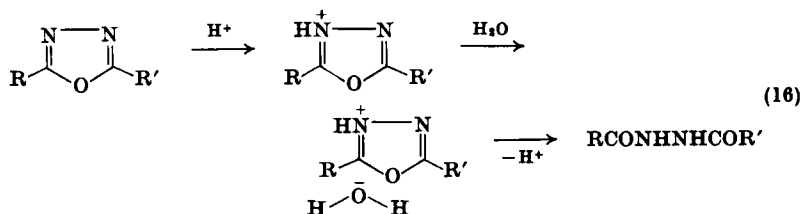
2-*o*-aminophenyl-1,3,4-oxadiazole (46) by formic acid, 3-amino-3,4-dihydroquinazol-4-one (47) is obtained. The reaction apparently proceeds via the open-chain hydrazine.<sup>69</sup>

<sup>127</sup> A. P. Grekov and O. P. Shvaika, *Stsintillyatory i Stsintillyats. Materialy Vses. Nauchn.-Issled. Inst. Khim. Reaktivov Materialy 2-go Koordinats. Sov.*, 1957, p. 105 (1960); see *Chem. Abstr.* **58**, 5662 (1963).

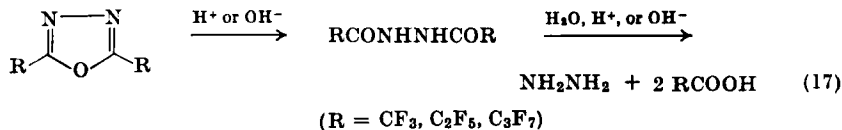
Very easy ring opening is also observed with the 2,5-dialkyl-1,3,4-oxadiazoles and the alkyl-substituted as well as the unsubstituted bis-1,3,4-oxadiazoles.

The acid hydrolysis of the 2-aryl-1,3,4-oxadiazoles can be used for their analytical determination. The method used is either to break down the compound by heating with hydrochloric acid under reflux to give the acid hydrazide and then to titrate the hydrazide with iodide in bicarbonate solution,<sup>68, 69</sup> or to titrate potentiometrically directly with sodium nitrite in a hydrochloric acid medium.<sup>128</sup> In this way the acid hydrazide is formed in the first reaction step and is then converted into the insoluble azide by the sodium nitrite.

The acid hydrolysis of the above 1,3,4-oxadiazole derivatives may in general be formulated in accordance with the following reaction mechanism [Eq. (16)]<sup>19</sup>:



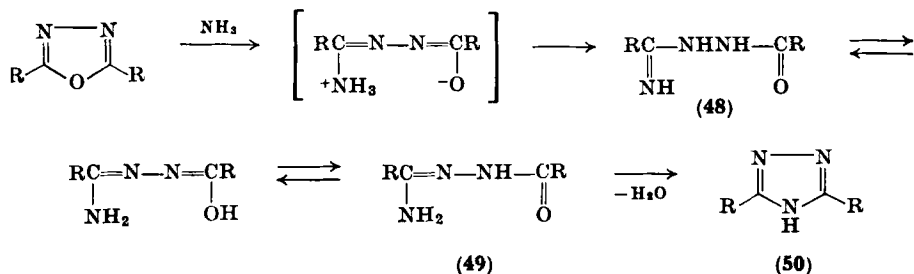
The 2,5-bisperfluoroalkyl-1,3,4-oxadiazoles, recently synthesized by Brown *et al.*,<sup>36</sup> show a particularly high sensitivity to nucleophilic attack, as could be expected because of the —I effect of the trifluoroalkyl groups.<sup>36, 129</sup> This contrasts with their extraordinarily high thermal stability. No decomposition could be observed either after 15 hours' heating at 350° or after 1 hour at 400°. Nevertheless they are hydrolyzed slowly by caustic soda to salts of perfluorocarboxylic acids and hydrolysis with concentrated sulfuric acid yields a mixture of the corresponding bisperfluoroacid hydrazides and the perfluorocarboxylic acids [Eq. (17)].<sup>36</sup>



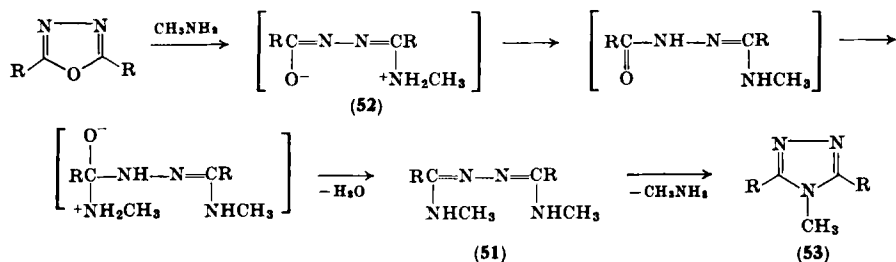
<sup>128</sup> A. P. Grekov and O. P. Shvaika, *Zh. Anal. Khim.* **15**, 731 (1960).

<sup>129</sup> H. C. Brown and M. T. Cheng, *J. Org. Chem.* **27**, 3240 (1962).

They are also cleaved by ammonia or methylamine,<sup>129</sup> like the 2,5-dialkyl-1,3,4-oxadiazoles.<sup>130</sup> Nucleophilic attack by ammonia apparently occurs at the ring C atom and produces the ring-opened intermediate 1-perfluoroacylimido-2-perfluoroacylhydrazines (48)



which have the tautomeric forms indicated. From the IR spectrum 49 is the most probable form in the solid state. 3,5-Bisperfluoroalkyl-1,2,4-triazoles (50) are obtained from these compounds by dehydration. The reaction of methylamine with 2,5-bisperfluoroalkyl-1,3,4-oxadiazoles either at room temperature or by heating under reflux yields only the symmetrical 1,2-bis-(*N*-methylperfluoroacylimido-2-perfluoroacylhydrazine (51). As a result of the greater nucleophilicity of methyl-



amine compared with ammonia, the 1-perfluoroacetylmethylimido-2-perfluoroacylhydrazines (52) cannot be isolated but react immediately by attack of a further mole of methylamine on the C=O group. 3,5-Bisperfluoroalkyl-4-methyl-1,2,4,4*H*-triazoles (53) may be obtained by elimination of methylamine from the 1,2-bis-(*N*-methylperfluoroacylimido-2-perfluoroacylhydrazines) formed in this way. IR and NMR

<sup>130</sup> R. Meyer, German Patent 574,944 (1933); see *Chem. Abstr.* **27**, 4373 (1933).

spectra have been taken of the above compounds and as far as possible the bands have been assigned.

Since the 1,3,4-oxadiazoles have recently achieved an increased significance pharmaceutically, the metabolism of 2-*m*- and 2-*p*-hydroxyphenyl-1,3,4-oxadiazole has also been investigated.<sup>131</sup> They are however, completely stable *in vivo*, in contrast to the relatively labile 1,3,4-oxadiazolinones,<sup>132</sup> and are incorporated into the organism as esters of sulfuric acid or of glucuronic acid.

## 2. Ring Cleavage of 2-Amino-1,3,4-oxadiazole

As with the above examples, the action of nucleophilic reagents on 2-amino-1,3,4-oxadiazoles leads to acyclic compounds which often cyclize immediately to triazoles. Thus 2-amino-1,3,4-oxadiazoles with caustic alkali yield 1,2,4-triazolinones.<sup>1, 59, 93, 133</sup> Careful hydrolysis of 2-amino-5-phenyl-1,3,4-oxadiazole with dilute Ba(OH)<sub>2</sub> or 4% NaOH yields 1-benzoylsemicarbazide which, with boiling NaOH solution, can be cyclized to 3-phenyl-1,2,4-triazolin-5-one.<sup>134</sup> This reaction has been carried out on an extended series of 2-amino-1,3,4-oxadiazole derivatives by heating for a short time with 10% caustic soda.<sup>64</sup> Thus the course of the reaction can be expressed as shown in Eq. (18).



Further nucleophilic reagents used to cleave 2-amino-1,3,4-oxadiazoles include alcoholic potash, primary amines, hydrazine hydrate, phenylhydrazine hydrochloride, acid hydrazides, semicarbazide, thiosemicarbazide, ammonium hydrogen sulfide, and hydrochloric acid.

A survey of the above-mentioned reactions will now be given. The alcoholysis<sup>135</sup> of 2-amino-1,3,4-oxadiazoles with alcoholic KOH yields 3-alkoxy-1,2,4-triazoles (**54**) from which 1,2,4-triazolin-5-ones may be prepared by heating with concentrated hydrochloric acid.

<sup>131</sup> A. M. El Masri, J. N. Smith, and R. T. Williams, *Biochem. J.* **68**, 587 (1958).

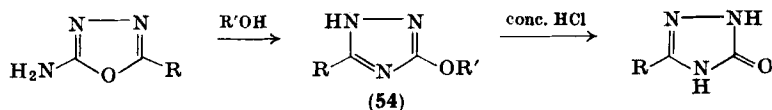
<sup>132</sup> S. Kakimoto, E. Krüger-Thiemer and E. Wempe, *Arzneimittel-Forsch.* **10**, 963 (1960).

<sup>133</sup> M. Girard, *Ann. Chim. (Paris)* [11] **16**, 326 (1941).

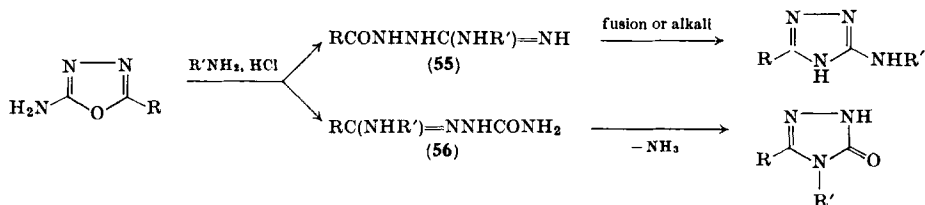
<sup>134</sup> G. Valenti and F. Maggio, *Ann. Chim. (Rome)* **42**, 18 (1952).

<sup>135</sup> H. Gehlen and G. Blankenstein, *Ann.* **651**, 128 (1962).

Using primary aromatic amine hydrochlorides in organic solvents, nucleophilic attack occurs, depending on the substituent,<sup>136</sup> either

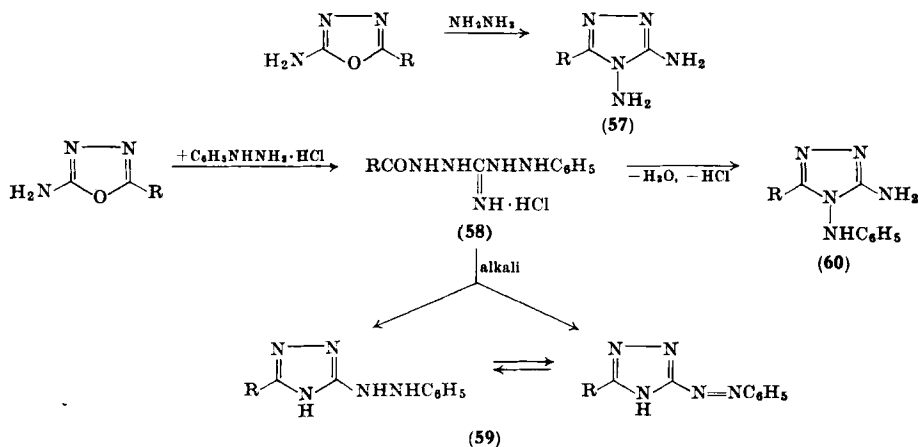


on the C-2 or the C-5 atom of the 2-amino-1,3,4-oxadiazole derivative. 1-Acylaminoguanidines (55) or 1-aryl-2-ureidoamidines (56) are



isolated. Both can be cyclized to the corresponding 1,2,4-triazole derivatives,<sup>137, 138</sup> which are also accessible directly by the action of aliphatic and aromatic amines on 2-amino-1,3,4-oxadiazoles.<sup>96, 138</sup>

In a similar manner 3,4-diamino-1,2,4-triazoles (57) are formed using



<sup>136</sup> H. Gehlen, J. Dost, and J. Cermak, *Ann.* **638**, 141 (1960).

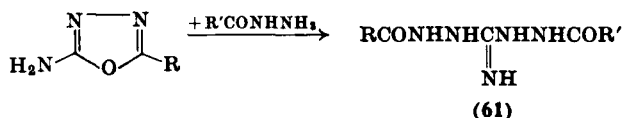
<sup>137</sup> H. Gehlen, J. Dost, and J. Cermak, *Ann.* **639**, 100 (1960).

<sup>138</sup> H. Gehlen and E. Benatzky, *Ann.* **615**, 60 (1958).

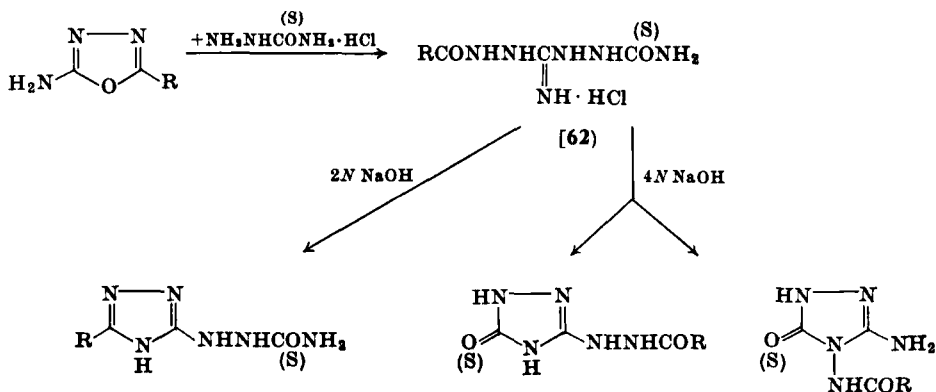
hydrazine hydrate.<sup>96, 139, 140</sup> Semicarbazides and carbohydrazide are produced as by-products. To some extent complete hydrolysis takes place to give carboxylic acids, hydrazine, ammonia, and CO<sub>2</sub>.

Reaction with phenylhydrazine hydrochloride<sup>141</sup> produces the isolable, ring-opened 1-acyl-5-phenyl-diaminoguanidine hydrochloride (**58**), the free base of which is partly oxidized even by atmospheric oxygen to 1-acyl-3-amino-5-phenylformazane. Cyclization of **58** with alkali produces arylhydrazino- or arylazo-1,2,4-triazoles (**59**); heating **58** in butanol produces 3,4-diamino-1,2,4-triazole (**60**).

1,5-Diacyldiaminoguanidines (**61**) are produced by the action of



acid hydrazides on 2-amino-1,3,4-oxadiazoles.<sup>142</sup> 1-Acyl-5-carbamoyl- or 1-acyl-5-thiocarbamoyldiaminoguanidine hydrochlorides (**62**) can be obtained by treatment in boiling alcohol solution with semicarbazide or thiosemicarbazide, respectively.<sup>143</sup> Treatment with sodium hydroxide solution produces, depending on the concentration used, either 3-aryl-5-semicarbazido-1,2,4-triazoles by elimination of water



SCHEME II

<sup>139</sup> H. Gehlen and G. Röbbisch, *Ann.* **663**, 119 (1963).

<sup>140</sup> H. Gehlen and H. Elchlepp, *Ann.* **594**, 14 (1955).

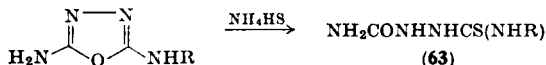
<sup>141</sup> H. Gehlen and G. Röbbisch, *Ann.* **665**, 132 (1963).

<sup>142</sup> H. Gehlen and N. Pollok, *Naturwiss.* **47**, 232 (1960).

<sup>143</sup> H. Gehlen and F. Lemme, *Naturwiss.* **50**, 645 (1963).

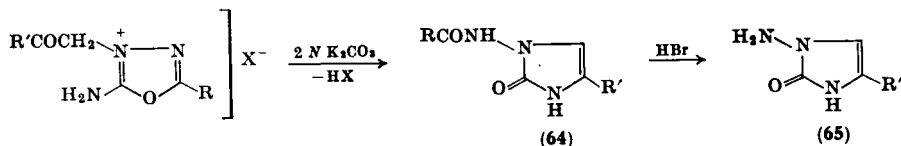
or 3-( $\beta$ -acylhydrazino)-1,2,4-triazolin-5-ones and 3-amino-4-acylamino-1,2,4-triazolin-5-ones by elimination of ammonia. The corresponding thio compounds can be obtained from 1-acyl-5-thiocarbamoyldiaminoguanidine hydrochloride (cf. Scheme II).

Ring hydrolysis of 2-amino-5-arylamino-1,3,4-oxadiazoles by ammonium hydrogen sulfide leads to the formation of 1-aryl-4-carbamoylthiosemicarbazide (63).<sup>98</sup> Arylhydrazine dicarboxamides



are formed when 2-amino-5-arylamino-1,3,4-oxadiazoles are treated with boiling hydrochloric acid.<sup>98</sup> The same reaction has been carried out on other substituted 2,5-diamino-1,3,4-oxadiazoles.<sup>126</sup> Hydrolysis with concentrated hydrochloric acid of 2-methyl-5-*p*-nitrophenylamino-1,3,4-oxadiazole or of its acetyl derivative produces *p*-nitroaniline and hydrazine dihydrochloride.<sup>102</sup>

Ring hydrolysis of 2-amino-1,3,4-oxadiazoles takes place under particularly mild conditions if the ring nitrogen is alkylated making the neighboring C atom positive. In this way 2-amino-3-phenacyl-1,3,4-oxadiazolium halides are cleaved by aqueous potassium carbonate even in the cold or at slightly raised temperatures. In this case ring rearrangement occurs with cyclization to give 1-acylamino-4-arylimidazolin-2-ones (64). From these compounds 1-amino-4-arylimidazolin-2-ones (65) can be synthesized by removal of the acyl group.<sup>123, 144</sup>



### 3. Ring Cleavage of 1,3,4-Oxadiazolin-5-ones and 1,3,4-Oxadiazolin-5-thiones

Just as in the case of the 1,3,4-oxadiazolium halides, ring cleavage of the 1,3,4-oxadiazolin-5-ones and -5-thiones can be achieved. These reactions using ammonia,<sup>145</sup> amines,<sup>145</sup> and hydrazine<sup>146</sup> have been

<sup>144</sup> H. Beyer and A. Hetzheim, *Ber.* **97**, 1031 (1964).

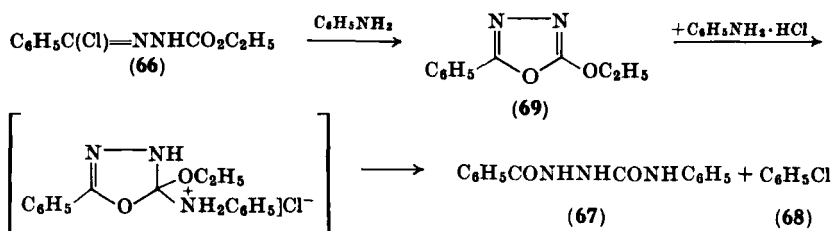
<sup>145</sup> A. Stempel, J. Zelauskas, and J. A. Aeschlimann, *J. Org. Chem.* **20**, 412 (1955).

<sup>146</sup> O. Diels and H. Okada, *Ber.* **45**, 2437 (1912); **46**, 1872 (1913).



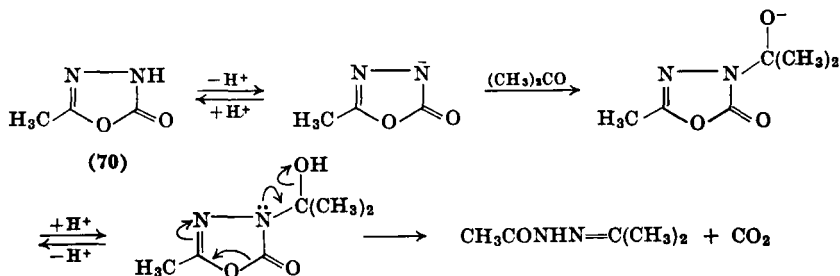
known for some time and have been more thoroughly investigated with some recently synthesized 1,3,4-oxadiazolinones, making use also of water, ethanol, and hydrazides as nucleophilic reagents. Thus by the action of alcoholic ammonia on 2-[3 $\alpha$ ,7 $\alpha$ ,12 $\alpha$ -trihydroxynorcholanyl-23]-1,3,4-oxadiazolin-5-one the ring-opened semicarbazide derivative can be isolated.<sup>87b</sup>

In the investigation of the reactions of halogenated hydrazones by Bacchetti,<sup>54</sup> 1-benzoyl-4-phenylsemicarbazide (67) and ethyl chloride



(68) were obtained by the action of aniline on  $\alpha$ -chlorobenzalcarbethoxyhydrazone (66). The course of the reaction can be explained in terms of the ring opening of 2-phenyl-5-ethoxy-1,3,4-oxadiazole (69) by the action of aniline hydrochloride, particularly since 2-phenyl-5-ethoxy-1,3,4-oxadiazole reacts with aniline hydrochloride in exactly this manner and the reaction has been carried out using completely anhydrous conditions.

Kurtz and Niemann<sup>147</sup> synthesized 2-methyl-4-benzyl-1,3,4-oxadiazolin-5-one and obtained from it 1-acetyl-2-benzylhydrazine carboxylic ester in good yield by the action of sodium ethoxide. 2-Methyl-1,3,4-oxadiazolin-5-one (70) exhibits an interesting behavior on neutralization in aqueous acetone solution. After beginning the

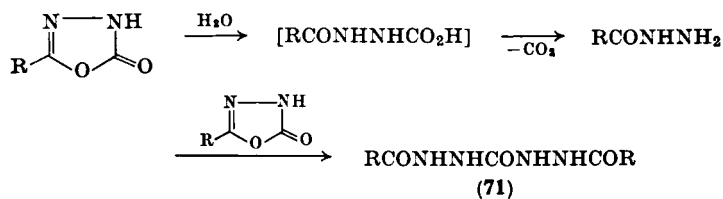


SCHEME III

<sup>147</sup> A. N. Kurtz and C. Niemann, *J. Org. Chem.* **26**, 1843 (1961).

neutralization a continuous addition of base is required to hold the pH constant at 7.9. The reaction is believed to proceed as in Scheme III. Thus 2-methyl-1,3,4-oxadiazolin-5-one can function as a buffer which can be destroyed *in situ* by the addition of an aldehyde or ketone.

From some 1,3,4-oxadiazolin-5-ones, such as 2-(2-furyl)-, 2-(2-nitro-5-furyl)-, 2-phenyl-, 2-(2-chlorophenyl)-, and 2-(4-pyridyl)-1,3,4-oxadiazolin-5-one, the corresponding 1,5-diacylcarbohydrazides can be obtained, the yield diminishing in the sequence given above. A relationship between the electron affinities of the substituents, the  $pK_a$  values of the 1,3,4-oxadiazolinones, and the ease of ring opening has not yet been established. The reaction path apparently proceeds via a hydrolytic ring opening with hydrazide formation and the hydrazide cleaves the remaining unchanged oxadiazolinone with formation of the 1,5-diacylcarbohydrazide (71). The fact that 1,5-



diacylcarbohydrazides are formed directly from 1,3,4-oxadiazolin-5-ones by the action of acid hydrazides supports this reaction mechanism. Further evidence for the proposed course of the reaction is that 1-(5-nitro-2-furoyl)-2-carbethoxyhydrazine is formed by heating 2-(2-nitro-5-(furyl)-1,3,4-oxadiazolin-5-one for 96 hours under reflux in ethanol. The rate-controlling step in the formation of the 1,5-diacylcarbohydrazides is the hydrolysis by water. The yield of the hydrolysis products increases as expected with increasing temperature and higher dielectric constant of the solvent. No ring cleavage of 2-(2-nitro-5-furyl)-1,3,4-oxadiazoline-5-thione is possible using either water or ethanol.

2-(2-Nitro-5-furyl)-, 2-(5-furyl)-, 2-(5-chlorophenyl)-, 2-phenyl-, and 2-(4-pyridyl)-1,3,4-oxadiazolin-5-one are cleaved by aliphatic and aromatic amines and by substituted hydrazines and hydrazides. Acylsemicarbazides or substituted carbohydrazides (72) are formed



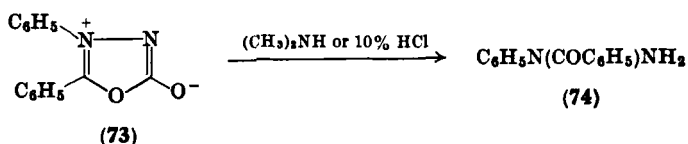
(72)



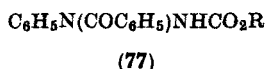
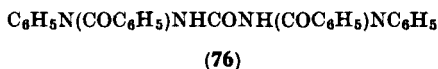
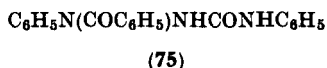
in this way.<sup>148</sup> 2-(2-Nitro-5-furyl)-1,3,4-oxadiazolin-5-thiones are less reactive than the corresponding substituted oxadiazolin-5-ones. Ring opening to the thiosemicarbazide derivatives is possible using *p*-toluidine, phenyl- and *p*-nitrophenylhydrazine, or thiocarbonylhydrazide.<sup>148</sup>

Investigations into the stability of 1,3,4-oxadiazolin-5-ones in metabolism are of particular interest since a series of oxadiazolinones, particularly those derived from isonicotinic acid hydrazide, have been used as drugs. 2-(4-Pyridyl)-1,3,4-oxadiazolin-5-one, after oral and intraperitoneal application to guinea pigs, appears, in addition to an unchanged fraction, as the following metabolites: isonicotinic acid hydrazide, *N*-isonicotinoyl-*N'*-acetylhydrazine, isonicotinic acid, and *N*-isonicotinoylglycine.<sup>132</sup> It could not be established how the ring cleavage occurs in the organism.

Hydrolytic ring-opening reactions occur extremely easily with the mesomeric betaine anhydro-5-hydroxy-2,3-diphenyl-1,3,4-oxadiazolium hydroxide (73).<sup>149</sup> Almost all the nucleophilic reagents so far



examined attack this compound with ring opening. Benzamide is formed using ammonia, and *N*-benzoyl-*N*-phenylhydrazine (74), isolable as the hydrochloride, using dimethylamine. This compound can also be obtained using 10% HCl. It is hydrolyzed by aqueous NaOH to benzoic acid and phenylhydrazine. Reaction with aniline produces 1-benzoyl-1,4-diphenylsemicarbazide (75).



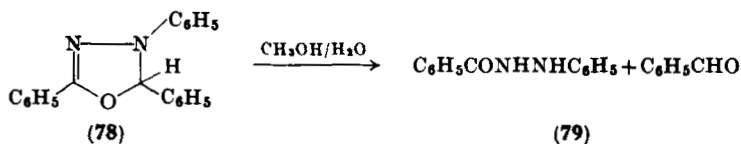
<sup>148</sup> W. R. Sherman and A. von Esch, *J. Org. Chem.* **27**, 3472 (1962).

<sup>149</sup> M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Japan* **34**, 668 (1961); see *Chem. Abstr.* **56**, 11580 (1962).

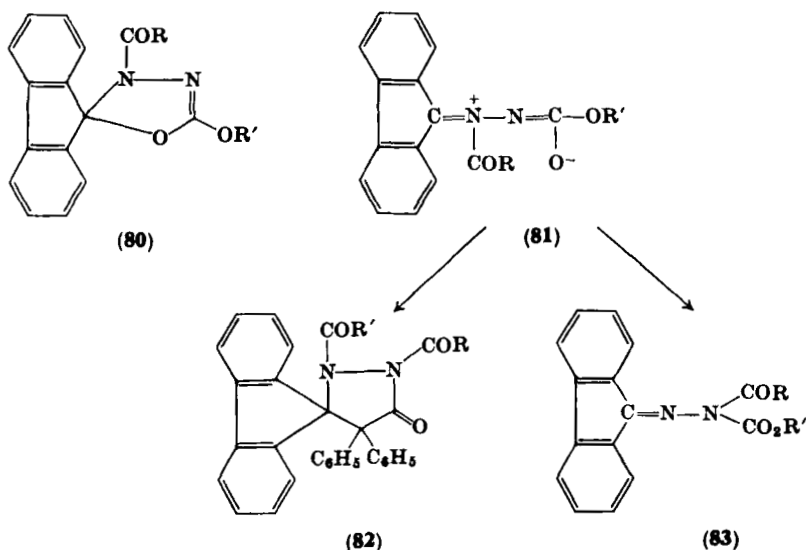
If one allows betaine (73) to react with *N*-benzoyl-*N*-phenylhydrazine, one obtains *N,N'*-dibenzanilidourea (76). The same compound is obtained by heating under reflux with water. *N*-Benzoyl-*N*-phenylhydrazinoformic ester (77) is formed using cyclohexanol and ethanol.

#### 4. Ring Cleavage of 1,3,4-Oxadiazolines and 1,3,4-Oxadiazolidines

Reduced 1,3,4-oxadiazoles very easily succumb to ring cleavage. 2,3,5-Triphenyl-2,3-dihydro-1,3,4-oxadiazole (78) is cleaved by boiling aqueous methanol to give benzoyl-2-phenylhydrazine (79) and benzaldehyde.<sup>107</sup> A very interesting ring chain isomerization is shown



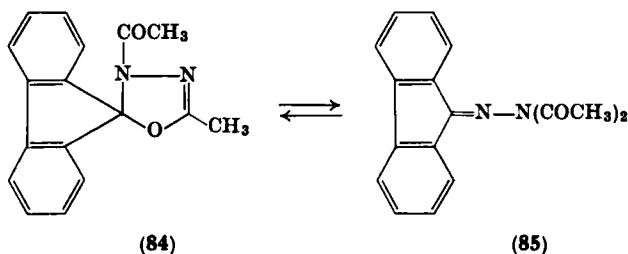
by the 2-(biphenylenyl)-3-acyl(or 3-carbalkoxy)-2,3-dihydro-1,3,4-oxadiazoles (80, R = R', OR').<sup>150</sup> In solution an equilibrium exists between the oxadiazoline form and the azomethine form (81). With



<sup>150</sup> E. Fahr, K. Döppert, and F. Scheckenbach, *Angew. Chem.* **75**, 670 (1963).

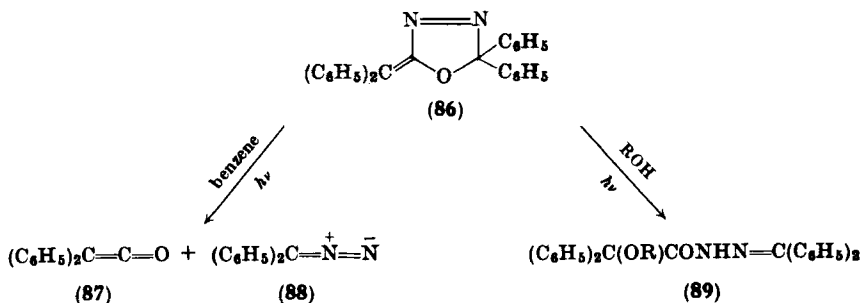
increasing dielectric constant of the solvent, the equilibrium shifts towards the azomethine form. This can be trapped by diphenylketene to yield **82**. Above 50° an irreversible rearrangement of 2-(biphenylenyl)-3-carbalkoxy-5-alkoxy-2,3-dihydro-1,3,4-oxadiazoles (**80** R = OR'') occurs to give the hydrazone dicarboxylic esters (**83**, R = OR'').

2-(Biphenylenyl)-3-acetyl-5-methyl-2,3-dihydro-1,3,4-oxadiazole (**84**) rearranges reversibly on warming to give the 2-(9-fluorenyl)-*N*-diacetylhydrazone (**85**). 2-(Biphenylenyl)-3-benzoyl-5-methyl-2,3-di-



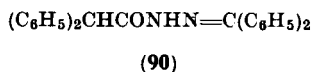
hydro-1,3,4-oxadiazole rearranges via the diacylhydrazone to 2-(biphenylenyl)-3-acetyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole. The latter compound and also 2-(biphenylenyl)-3-benzoyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole are very stable.

Easy photolysis of 1,3,4-oxadiazolines to give the starting materials has been observed in the case of 2,2-diphenyl-5-diphenylmethylen-1,3,4-oxadiazoline (**86**).<sup>114</sup> Diphenylketene (**87**) and diphenyldiazo-

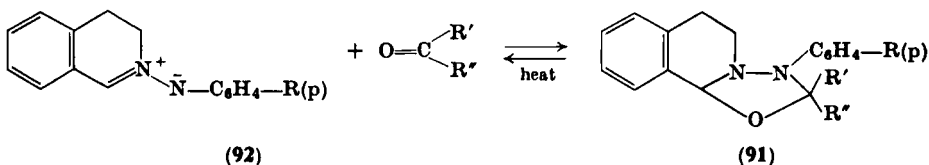


methane (**88**) are obtained. With UV light carboxylic acids and alcohols are immediately added with the formation of **89**. Ring opening

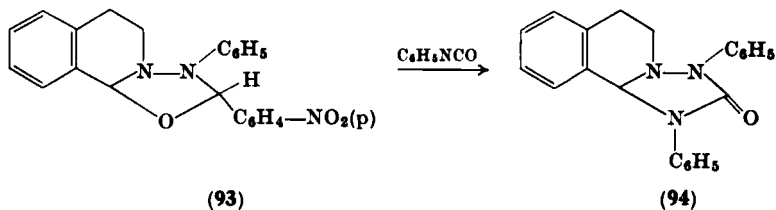
of 2,2-diphenyl-5-diphenylmethylene-1,3,4-oxa-diazoline occurs on catalytic hydrogenation using Raney nickel. The reaction appears to proceed via an oxadiazolidine which easily rearranges to **90**.



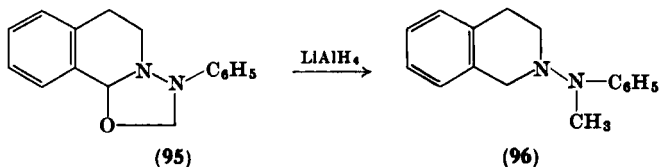
The 1,3,4-oxadiazolidines (**91**) prepared by Grashey and Adelsberger<sup>110</sup> using a 1,3-dipolar addition are also extremely thermolabile.



They are decomposed by this means to their starting materials, the azomethanimines of 3,4-dihydroisoquinoline (**92**), and the carbonyl compound. This is recognizable by a color change to reddish-brown. Acid hydrolysis of **91** produces the hydrazonium salt of **92** and the



carbonyl compound. The compound **93**, after decomposition, adds to phenylisocyanate to form the 1,2,4-triazolidinone derivative (**94**). The reaction of the oxadiazolidine (**95**) with  $\text{LiAlH}_4$  leads to 2-(phenylmethylamino)-1,2,3,4-tetrahydroisoquinoline (**96**).



#### IV. Physical Properties of 1,3,4-Oxadiazoles

In recent years molecular, electronic, and nuclear resonance spectra have been increasingly drawn upon in the elucidation of the structures of 1,3,4-oxadiazole derivatives.

In the IR field, the oxadiazole ring has been characterized primarily by the bands at about  $970\text{ cm}^{-1}$ ,<sup>37, 151</sup>  $1020\text{--}1030\text{ cm}^{-1}$ ,<sup>59, 151</sup> due to the C—O bond and at  $1560\text{--}1640\text{ cm}^{-1}$ ,<sup>35, 36, 44a, 55, 65, 151, 152</sup> due to the C=N valence vibration. 2,5-Dialkyl derivatives in this case fall in the longer-wavelength region<sup>35, 36, 44a, 151</sup> and oxadiazoline thiones in the shorter-wavelength region.<sup>65</sup> The C=O absorption in 1,3,4-oxadiazolin-5-ones lies at  $1740\text{--}1785\text{ cm}^{-1}$  even in condensed systems.<sup>76, 78, 116</sup>

The bands of the alkylated and acetylated derivatives which were investigated lie in the same area<sup>76, 78</sup> so that here too the tautomeric structure 5-hydroxy-1,3,4-oxadiazole is ruled out. The same is true for the 1,3,4-oxadiazoline-5-thiones. The presence of C=S bands at  $1300\text{--}1325\text{ cm}^{-1}$  or  $1350\text{--}1370\text{ cm}^{-1}$ , C—NH bands at  $1438\text{--}1538\text{ cm}^{-1}$ , as well as NH vibrations at  $3165$  and  $3450\text{ cm}^{-1}$ , is only compatible with a thione structure.<sup>65, 78</sup> As can be concluded from the IR data, the 1,3,4-oxadiazoline-5-thiones exist in a monomer-dimer equilibrium.<sup>65</sup> 2-Amino-1,3,4-oxadiazoles are characterized variously by a doublet of N—H bands near  $3100\text{ cm}^{-1}$  and above  $3200\text{ cm}^{-1}$ .<sup>59, 62, 63</sup> The medium-strong bands at  $1640\text{--}1670\text{ cm}^{-1}$  are also assigned to the amino groups.<sup>95</sup> With substitution at the amino group the maxima are shifted to longer wavelengths.<sup>39, 42, 63</sup> The methylation products derived from 2-amino-5-phenyl-1,3,4-oxadiazole are 2-imino-1,3,4-oxadiazolines on the basis of the strong bands at  $1680$  or  $1710\text{ cm}^{-1}$ .<sup>63</sup> 3,5-Diphenyl-2-arylimino-1,3,4-oxadiazolines show maxima in the same region.<sup>109</sup>

The 1,3,4-oxadiazole system has an electronic spectrum equivalent to that of benzene and the maxima of the oxadiazole derivatives are only slightly shifted hypsochromically compared with benzene.<sup>103</sup> Thus, for example, diphenyl and 2-phenyl-1,3,4-oxadiazole absorb almost identically at  $248\text{ m}\mu$  and *p*-terphenyl and 2,5-diphenyl-1,3,4-oxadiazole absorb at  $276$  and  $280\text{ m}\mu$ , respectively.<sup>103</sup> The oxadiazole system is effective in the conjugative transmission of the effects of substituents.<sup>103</sup> An extension of the system of conjugated  $\pi$  bonds

<sup>151</sup> M. Milone and E. Borello, *Gazz. Chim. Ital.* **81**, 677 (1951).

<sup>152</sup> J. Barrans, *Compt. Rend.* **249**, 1096 (1959).

leads, as expected, to a shift of the absorption spectra to longer wavelengths.<sup>103, 153</sup> The maximum for 2,5-di-(1-naphthyl)-1,3,4-oxadiazole is at 335 m $\mu$ ; for 2-biphenyl-5-phenyl-1,3,4-oxadiazole it is at 300 m $\mu$ , compared with the value given above of 280 m $\mu$  for 2,5-diphenyl-1,3,4-oxadiazole.<sup>154</sup> Similar shifts to longer wavelengths are also caused by increase in the degree of conjugation of oxadiazolinone derivatives. Pyrido[2,1-*b*]1,3,4-oxadiazolin-2-ones absorb at 290–305 m $\mu$ , whereas quinolino[2,1-*b*]1,3,4-oxadiazolin-2-one absorbs with about the same intensity at 325 m $\mu$ .<sup>116</sup> 2,2,5-Trisubstituted 3-acyl-1,3,4-oxadiazolines have a maximum at 241 m $\mu$  for the trimethylated acetyl derivative and maxima at 290, 292, and 305 m $\mu$  for the phenyl-substituted compounds.<sup>46</sup> The small bathochromic shift of mono- and dimethylamino derivatives (283 and 290 m $\mu$ )<sup>63</sup> compared with 2-amino-5-phenyl-1,3,4-oxadiazole (277–278 m $\mu$ )<sup>62, 63</sup> is offered as evidence for the dominance of the amino form in the tautomeric amino-imino equilibrium. The comparable mono- and dimethylated 5-phenyl-2-imino-1,3,4-oxadiazolines absorb at 293 and 302 m $\mu$ .<sup>63</sup> Polymeric 1,3,4-oxadiazoles which are linked by phenylene groups still absorb in almost the same region, despite a color change resulting from several hours' heating at a temperature above 400°. The strong absorption of many 1,3,4-oxadiazole derivatives and the possibility of producing a shift into a particular UV region by special substituents has been made a basis for various procedures for the preparation of light filters (cf. Section V).

2,5-Diaryl-1,3,4-oxadiazoles exhibit strong fluorescence in solution on stimulation by UV or  $\beta$ -irradiation, particularly 2-biphenyl-5-phenyl- and 2-biphenyl-5-(1-naphthyl)-1,3,4-oxadiazole (cf. Section V). The quantum yield of the 1,3,4-oxadiazoles is lower than with *p*-terphenyl and its analogs.<sup>153–155</sup> The band intensity with unsubstituted aryl-1,3,4-oxadiazoles and aromatic substituted oxadiazoles is essentially the same.<sup>155</sup>

In some cases for particular oxadiazole derivatives, such as poly-fluoroalkyloxadiazoles<sup>85</sup> and derivatives of 5-phenyl-1,3,4-oxadiazoline,<sup>115</sup> nuclear magnetic resonance spectra have been utilized for characterization and clarification of the structure.

<sup>153</sup> L. M. Kutsyna and E. T. Verkhovtseva, *Opt. i Spektroskopiya* **12**, 785 (1962).

<sup>154</sup> Yu. N. Panov, N. A. Adrova, and M. M. Koton, *Opt. i Spektroskopiya* **7**, 29 (1959).

<sup>155</sup> L. M. Kutsyna, R. P. Sidorova, L. V. Voevoda, J. K. Ishchenko, and J. P. Demčenko, *Izv. Akad. Nauk SSSR, Ser. Fiz.* **26**, 1304 (1962).



Few  $pK$  values of 1,3,4-oxadiazoles have been measured, partly because of the poor water solubility of aromatic substituted oxadiazoles. A  $pK_b$  value of 11.63 (in water) is given for 2-amino-5-methyl-1,3,4-oxadiazole.<sup>156</sup> 2-Amino-5-phenyl-1,3,4-oxadiazole and its mono- and dimethylamino derivatives have approximate  $pK_a$  values between 2.3 and 2.7 (in 50% alcohol).<sup>63</sup> On the other hand, the  $pK_a$  values of 2-imino-3-methyl-5-phenyl-1,3,4-oxadiazoline and of 2-methylimino-3-methyl-5-phenyl-1,3,4-oxadiazoline are 6.31 and 6.38, respectively.<sup>63</sup>

## V. Uses of 1,3,4-Oxadiazoles

The growing patent literature of recent years demonstrates that the 1,3,4-oxadiazoles are becoming of great practical significance. This concerns primarily drug syntheses, the production of polymers, the preparation of dyes, and uses in photography, as light screening agents, and as scintillators.

A group of 1,3,4-oxadiazolin-5-ones and 1,3,4-oxadiazoline-5-thiones show antitubercular activity.<sup>18, 43a, 76, 84-86, 131, 132, 157-160</sup> They have been investigated with regard to their mode of action. 2-(4'-Pyridyl)-1,3,4-oxadiazolin-5-one (S 57) has shown itself active against *Mycobacterium tuberculosis* and *Mycobacterium leprae*.<sup>85, 158</sup> It possesses some advantages compared with isonicotinic acid hydrazide. Derivatives of S 57 also have some tuberculostatic activity.<sup>159, 161, 162</sup> Further tuberculostatic compounds are derived from *p*-aminosalicylic acid, for example WS 127 [2-(4'-amino-2'-hydroxyphenyl)-1,3,4-oxadiazoline-5-thione] and WS 174 [2-(4'-acetamido-2'-hydroxyphenyl)-1,3,4-oxadiazolin-5-one].<sup>85</sup> 2-Cyanomethyl-1,3,4-oxadiazolin-5-one shows a tuberculostatic activity comparable with that of "Reazid."<sup>18</sup> Oxadiazolin-5-ones and oxa-

<sup>156</sup> H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.* **77**, 4076 (1955).

<sup>157</sup> S. Kakimoto, *Tuberk.-Forschungsinst. Borstel Jahresber.* **5**, 233 (1961); see *Chem. Abstr.* **57**, 15609 (1962); P. Picart, *Chemothérapie* **3**, 53 (1961).

<sup>158</sup> A. E. Wilder Smith and H. Brodhage, *Nature* **192**, 1195 (1961).

<sup>159</sup> A. E. Wilder Smith, U.S. Patent 2,758,117 (1956); see *Chem. Abstr.* **51**, 3670 (1957).

<sup>160</sup> H. Erlenmeyer, British Patent 945,910 (1964); see *Chem. Abstr.* **60**, 10692 (1964).

<sup>161</sup> A. E. Wilder Smith, Swiss Patent 322,065 (1957); see *Chem. Abstr.* **52**, 1560 (1958).

<sup>162</sup> E. Geistlich Söhne A.G., British Patent 771,809 (1957); see *Chem. Abstr.* **52**, 1273 (1958).

diazoline-5-thiones also possess variously analgetic, antipyretic, and antiphlogistic properties.<sup>87, 163</sup> The 2-[5'-nitrofuryl-(2')]-1,3,4-oxadiazolin-5-ones have been thoroughly investigated as fungicidal and bactericidal agents.<sup>78, 81, 163a</sup> 1-Trichloromethylmercapto-1,3,4-oxadiazolin-5-ones are also used as fungicides agriculturally.<sup>121</sup> 2-Amino-5-phenyl-1,3,4-oxadiazole and 2-phenyl-1,3,4-oxadiazolin-5-one<sup>164</sup> have anti-convulsive and paralytic activity, while 2-hydroxyphenyl-1,3,4-oxadiazole acts as an hypnotic and sedative.<sup>66, 69, 70</sup> 2-(*o*-Alkoxyphenyl)-1,3,4-oxadiazoles are also used as X-ray contrast materials.<sup>87</sup> The sulfonamide derivatives of 1,3,4-oxadiazole are established not only as bactericides but also as hypoglycemic agents.<sup>124, 125, 165</sup> An interesting use of 2-furyl- and 2-phenyl-1,3,4-oxadiazoline-5-thione is as a chlorination inhibitor during tetracycline synthesis.<sup>166</sup>

1,3,4-Oxadiazoles are acquiring greater significance in the stabilizing<sup>167</sup> and preparation of macromolecular materials.<sup>38, 168</sup> Thus poly-1,3,4-oxadiazoles with aliphatic substituents are used as films, although aryl derivatives can be used neither as fibres nor films. The high thermal stability of these compounds is worthy of note.

The 2,5-perfluoroalkyl-1,3,4-oxadiazoles show an extraordinarily high thermal stability. Among other possible applications, they can be used as bath liquids and solvents for highly fluorinated polymers.<sup>35</sup>

In the last few years numerous 1,3,4-oxadiazole derivatives

<sup>163</sup> A. E. Wilder Smith, E. Frommel, and S. Radouco-Thomas, *Arzneimittel-Forsch.* **13**, 338 (1963).

<sup>163a</sup> H. Saikachi, German Patent 1,171,927 (1962); see *Chem. Abstr.* **61**, 5664 (1964); W. R. Sherman, U.S. Patent 3,024,233 (1962); see *Chem. Abstr.* **57**, 11204 (1962); H. Inoue and A. Saikachi, Japanese Patent 20,572 (1963); see *Chem. Abstr.* **60**, 2952 (1964).

<sup>164</sup> G. Maffii, E. Testa, and R. Fusco, *Farmaco (Pavia), Ed. Sci.* **13**, 629 (1958); G. L. Hassert Jr., J. W. Plutsiaka, D. Papandrianos, J. C. Burke, and B. N. Craver, *Toxicol. Appl. Pharmacol.* **3**, 726 (1961).

<sup>165</sup> J. B. O'Neal, *Chem. Eng. News* p. 56 (1960); J. B. O'Neal, H. Rosen, P. B. Russell, A. C. Adams, and A. Blumenthal, *J. Med. Pharm. Chem.* **5**, 617 (1962); see *Chem. Abstr.* **57**, 9168 (1962); Am. Cyanamid Co., French Patent 72,707; 3rd additional patent to Patent 1,034,958 (1960).

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<sup>167</sup> H. Pohlemann, H. Weber, and A. Stassen, German Patent 1,116,897 (1960); see *Chem. Abstr.* **56**, 6172 (1962); H. Pohlemann, H. Burger, and O. Leichtle, British Patent 908,214 (1962); see *Chem. Abstr.* **58**, 2551 (1963).

<sup>168</sup> A. H. Frazer, Japanese A.S. 3,899 (1961); French Patent 1,259,570 (1961); see *Chem. Zentr.* **1**, 275/2650 (1964).

have been patented as dyestuffs, particularly anthraquinone vat dyes<sup>10, 71, 72, 169</sup> and azo dyes.<sup>14, 17, 170</sup>

Various 1,3,4-oxadiazoles are suitable for use in photography as tone improvers,<sup>171</sup> as development accelerators,<sup>172</sup> and as photoelectrically sensitive materials for coatings in electrographic reproduction processes.<sup>7, 173</sup> In the last case one makes use of the sensitivity of many oxadiazole derivatives to UV light and produces the displacement to the visible region by addition of sensitizing dyes.

The convenient UV absorption region of 2,5-diaryl-1,3,4-oxadiazoles enables them to be used as light-screening agents and optical brighteners.<sup>8, 9, 12, 13, 174</sup>

The scintillation properties of 1,3,4-oxadiazoles have been particularly intensively investigated since 1955.<sup>154, 175-191</sup> Liquid and plastic

<sup>169</sup> Ciba, French Patent 1,287,017 (1961); see *Chem. Zentr.* **31**, 259/2437 (1964); Belgian Patent 610,864 (1962); see *Chem. Abstr.* **58**, 4674 (1963); Israeli A.S. 16,721 (1963); see *Chem. Zentr.* **21**, 249/2415 (1964); Belgian Patents 631,054 and 633,827 (1963); see *Chem. Abstr.* **61**, 1983 and 1985 (1964).

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<sup>172</sup> K. Futaki, *Nippon Shashin Gakkai Kaishi* **24**, 60 (1961); see *Chem. Abstr.* **56**, 11109 (1962).

<sup>173</sup> Kalle A.G., British Patent 940,273 (1963); see *Chem. Abstr.* **60**, 4992 (1964); Kalle A.G., British Patent 951,106 (1964); see *Chem. Abstr.* **61**, 2637 (1964).

<sup>174</sup> A. E. Siegrist (Ciba), Swiss Patent 366,837 (1963); *Chem. Abstr.* **60**, 2953 (1964); H. Krzikalla, H. Pohlemann, and K. E. Kling (BASF), German Patent 959,402 (1957).

<sup>175</sup> J. C. Roucayrol, E. Oberhauser, and R. Schussler, *Nucleonics* **15**, No. 11, 104 (1957); U. Nay, H. J. Eichhoff, G. Herrmann, and H. O. Wirth, *Z. Elektrochem.* **64**, 1098 (1960).

<sup>176</sup> R. C. Minehart and R. H. Milburn, *Rev. Sci. Instr.* **31**, 173 (1960).

<sup>177</sup> L. M. Bollinger, H. Palensky, J. Ise, Jr., J. E. Brolley, C. L. Cowan, Jr., B. C. Diven, and T. W. Bonner, *Proc. 1st Intern. Conf. Peaceful Uses At. Energy, Geneva, 1955* Vol. **4**, p. 47. Columbia Univ. Press (I.D.S.), New York, 1956; D. L. Williams, F. N. Hayes, R. L. Schuch, R. L. Crawford, and

scintillators are being introduced in increasing quantities for the measurement of weak  $\beta$ -rays,<sup>175</sup> of ionized particles in cosmic radiation,<sup>176</sup> and of  $\gamma$ -rays and fast neutrons,<sup>177</sup> since only simple counting apparatus is required. However, the relatively small photon yield of these scintillators compared with the dark current of the photomultiplier has made it necessary to search for very active scintillation materials. The best scintillators so far known include 2-phenyl-5-biphenyl-1,3,4-oxadiazole (PBD), (relative impulse height 1.28) and 2-(4-biphenyl)-5-(1-naphthyl)-1,3,4-oxadiazole (LNBD).<sup>178</sup> Although the relative impulse height using 2-biphenylenyl-5-phenyl-1,3,4-oxadiazole is not as high as that using the biphenyl compound,

- R. D. Hiebert, *U.S. At. Energy Comm. Rept.* No. LA-2375, p. 59 (1960); see *Chem. Abstr.* **54**, 14993 (1960).
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- <sup>180</sup> L. M. Kutsyna and E. T. Verkhovtseva, *Opt. i Spektroskopiya* **12**, 785 (1962).
- <sup>181</sup> A. Coche, R. Henck, and G. Laustriat, *Compt. Rend.* **247**, 2123 (1958); H. K. Bothe, *Ann. Physik* [7] **6**, 156 (1960).
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- <sup>186</sup> F. H. Brown, M. Furst, and H. P. Kallmann, *Discussions Faraday Soc.* **27**, 43 (1959).
- <sup>187</sup> E. A. Andreeshchev and I. M. Rozman, *Opt. i Spektroskopiya* **8**, 828 (1960).
- <sup>188</sup> E. A. Andreeshchev, E. E. Baroni, K. A. Kovyrzina, I. M. Rozman, and W. M. Schoniya, *Izv. Akad. Nauk SSSR, Ser. Fiz.* **22**, 67 (1958).
- <sup>189</sup> N. P. Shimanskaya, A. P. Kilimov, A. P. Grekov, L. M. Egupova, and R. S. Azen, *Opt. i Spektroskopiya* **7**, 366 (1959).
- <sup>190</sup> N. P. Shimanskaya and V. D. Bezuglyi, *Zh. Obshch. Khim.* **33**, 1726 (1963).
- <sup>191</sup> A. Fort, *Prokroky Mat. Fys. Astron.* **3**, 161 (1958).

lower concentrations are possible.<sup>31</sup> Detailed publications are available concerning the connection between the structure and the scintillation properties of the 1,3,4-oxadiazoles.<sup>154, 179</sup> In general, electron donors and extension of the conjugation increase the scintillation activity. Furthermore the solvent has an influence on the scintillation, particularly also with the addition of substances as wave shifters.<sup>179-181</sup> Oxygen has a quenching effect.<sup>182, 183</sup>

Numerous new 1,3,4-oxadiazole derivatives have been synthesized for all the investigations in this field.<sup>12, 19, 20, 23, 67</sup>

# The Literature of Heterocyclic Chemistry

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## I. Introduction and General Discussion

### A. SCOPE AND ARRANGEMENT

The original literature of heterocyclic chemistry is enormous, and is rapidly increasing. Many reviews and monographs are available which are of great assistance to the research worker, but they are scattered over a very wide range of journals and publishers. In this article we attempt to list all books, review chapters, and articles published over the last twenty years or so which deal, exclusively or mainly, with heterocyclic chemistry. We believe that this will be of assistance to researchers and teachers whose activities take them into the heterocyclic field.

We have attempted to arrange the articles in a logical order by subjects. The following criteria are used to do this: (a) the ring size, (b) the number of hetero atoms in the ring, (c) the orientation of the hetero atoms, (d) the nature of the hetero atoms, (e) the degree of unsaturation in the ring, (f) the topic discussed in the article.

Within each subsection, articles are arranged in date order, commencing with the most recent.

Some general sources and those articles covering topics which cut right across the above system of arrangement are listed in the next subsection. Final sections cover both those heterocyclic compounds involving "unusual" hetero atoms (by which is meant any hetero atom other than carbon, nitrogen, oxygen, or sulfur), and alkaloids, drugs, pigments, etc.

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- R. Rambaud, General properties of oxygen-containing heterocyclic compounds. In "Traité de chimie organique" (V. Grignard *et al.*, eds.), Vol. 18, p. 36. Masson, Paris, 1945.
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G. Spielberger *et al.*, In "Methoden der organischen Chemie" (Houben-Weyl, eds.), Vol. 11, Part 1, p. 24. Thieme, Stuttgart, 1957.

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H. A. Hageman, *Org. Reactions* **7**, 198 (1953).

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Spectra of some dyes and indicators, effect of salts and proteins:

I. M. Klotz, *Chem. Rev.* **41**, 373 (1947).

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W. R. Brode, *In* "Roger Adams Symposium" p. 8, Wiley, New York, 1955.

Synthesis:

T. Holbro, *Chimia (Aarau)* **8**, 57 (1954).



# Mass Spectrometry of Heterocyclic Compounds

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## I. Introduction

### A. PRINCIPLES

Mass spectrometry is rather different from other spectroscopic methods such as IR or UV spectroscopy. The common feature of all spectroscopic methods, including MS, is an excitation of the molecules under investigation. In all spectroscopic methods other than mass spectrometry, the absorbed excitation energy is measured and used to make statements about the presence of special groups or bonds. After this physical measurement the substance may be recovered unchanged.

In the ion source of a mass spectrometer the molecule is excited by electron impact. The attacking electrons, usually having an energy of about 70 eV, transfer to the molecules an inexactly defined amount of energy, which is usually enough to ionize them and to break them into fragments. Thus a molecule undergoes in the ion source of the mass spectrometer a real chemical degradation which does not permit recovery of the material. The charged degradation products, usually

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only the positive ones, are separated with the aid of electrical and magnetic fields and registered according to their mass to charge ( $m/e$ ) ratio. A mass spectrum therefore does not show absorption energies, but the mass<sup>1</sup> and amount of the produced (positively) charged ions.

## B. REQUIREMENTS FOR A MASS SPECTROMETRIC ANALYSIS

Mass spectra can only be obtained from compounds which are in the vapor-phase. The vapor pressure required to obtain a spectrum depends on the kind of sample introduction system: if the sample is first evaporated in the gas container of the spectrometer and from there introduced into the ion source, a vapor pressure of about  $10^{-2}$  mm Hg is necessary, while for direct introduction of the substance into the ion source a vapor pressure of only  $10^{-6}$  mm is needed,<sup>2</sup> usually sufficient to obtain spectra of very polar and nearly nonvolatile compounds, e.g., amino acids. Therefore, direct introduction systems<sup>2-9</sup> (see also Biemann,<sup>10</sup> p. 33) available since the pioneering work of Reed<sup>2</sup> in all commercial instruments should be used in spite of experimental difficulties, if thermal or catalytic decomposition of the sample is to be expected. If the vapor pressure is so low that the sample cannot be vaporized sufficiently in the ion source, protecting of polar OH and NH groups by methylation or acetylation may produce a derivative of volatility enough to obtain a spectrum.

<sup>1</sup> Usually particles with only one positive charge are produced and doubly-charged ions commonly do not play an important role in the interpretation of spectra. Therefore the simplified expression "mass" is used instead of the correct expression  $m/e$ .

<sup>2</sup> R. I. Reed, *J. Chem. Soc.* p. 3432 (1958); P. A. Finan and R. I. Reed, *Nature* **184**, 1866 (1959).

<sup>3</sup> H. J. M. Fitches, in "Advances in Mass Spectrometry" (R. M. Elliott, ed.), Vol. 2, 428. Pergamon Press, Oxford, 1963.

<sup>4</sup> G. Spiteller, C. Brunnée, K. Heyns, and H. F. Grützmacher, *Z. Naturforsch.* **17b**, 856 (1962).

<sup>5</sup> K. Heyns and H. F. Grützmacher, *Angew. Chem.* **74**, 387 (1962).

<sup>6</sup> C. Brunnée, *Z. Instrumentenk.* **68**, 97 (1960).

<sup>7</sup> J. F. Lynch, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Experientia* **19**, 211 (1963).

<sup>8</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **94**, 742 (1963).

<sup>9</sup> J. H. Beynon, R. A. Saunders, and A. E. Williams, *Appl. Spectry.* **17**, 63 (1963).

<sup>10</sup> K. Biemann, "Mass Spectrometry, Organic Chemical Applications." McGraw-Hill, New York, 1962.

Besides nonvolatility, the resolving power of the available single-focusing instruments limits the applications of MS to compounds of a molecular weight up to a maximum of about 1,200. Technical improvements and the new double-focusing instruments will probably raise this limit in the near future.

The amount of sample required to obtain a spectrum is of the order of 0.01 mg (direct sample introduction system) to 1 mg (indirect sample introduction system). Purity of the sample is desirable, but in many cases not essential. Usually up to 10% of impurity (much more even of low molecular weight compounds) does not seriously interfere with the interpretation. In some instances, information about the structures of the different compounds may be obtained even from mixtures.

### C. CORRELATIONS BETWEEN MASS SPECTRUM AND STRUCTURE

There are many monographs available which deal with the correlations between structure and mass spectra.<sup>10-17</sup> The books of Biemann<sup>10</sup> and Budzikiewicz, Djerassi, and Williams,<sup>11</sup> in particular, contain excellent surveys of this topic. Nevertheless a brief discussion of the main mass spectrometric fragmentation laws may be a useful introduction for the present chapter.

The main degradation routes of the primarily produced molecular ion are those which require the lowest amount of energy. Therefore the weakest bonds are cleaved and the most stable degradation products are formed preferentially, because in these cases the energy

<sup>11</sup> H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden Day, San Francisco, 1964.

<sup>12</sup> F. W. McLafferty (ed.), "Mass Spectrometry of Organic Ions." Pergamon Press, Oxford, 1963.

<sup>13</sup> J. H. Beynon, "Mass Spectrometry and its Application to Organic Chemistry." Elsevier, Amsterdam, 1960.

<sup>14</sup> R. I. Reed, "Ion Production by Electron Impact." Academic Press, New York, 1962.

<sup>15</sup> F. W. McLafferty, in "Determination of Organic Structures by Physical Methods" (F. C. Nachod and W. D. Phillips, eds), Vol. 2, p. 93ff. Academic Press, New York, 1961.

<sup>16</sup> F. W. McLafferty, "Mass Spectral Correlations." Am. Chem. Soc., Washington, D.C., 1963.

<sup>17</sup> G. Spiteller, "Massenspektrometrische Strukturanalyse organischer Verbindungen: Eine Einführung" Verlag Chemie, Heidelberg, 1966.

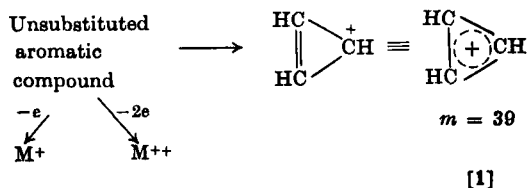
needed for bond fission may be partly compensated by the gain in stabilization energy.

If a molecule contains only bonds of nearly equal strength and the degradation products are not of different stability (e.g., in saturated unbranched hydrocarbons), the probability of cleaving any of a number of bonds is also nearly equal. Therefore no special fission is favored: the mass spectra of those compounds show many peaks, and their interpretation is sometimes difficult. In contrast to this, molecules possessing hetero atoms or aromatic rings have bonds of different strengths and in addition the positive charge of some degradation products can be often stabilized very well by resonance with the unpaired electrons of the hetero atom or the  $\pi$  electrons of the aromatic system. Therefore specific fission reactions are favored, and these produce only a few ions with high probability. The mass spectra of such compounds are marked by a small number of very intense peaks, corresponding to fragments which can be correlated with special features of the compound under investigation.

Heterocyclic compounds contain hetero atoms and very often aromatic systems also. They fulfil, therefore, the conditions for the production of characteristic mass spectrometric fragmentation patterns. For this reason mass spectrometry has become especially valuable for structural investigations in this class of compounds.

## II. Mass Spectra of Simple Heterocyclic Molecules

The spectra of unsubstituted heterocyclic compounds are characterized by very intense peaks of the molecular ions. The elimination of one electron from their rich stock of  $\pi$  electrons requires only a very



small amount of energy compared with the energy needed for further decomposition, which is not possible without cleavage of the ring system. Expulsion of even two electrons occurs fairly readily, especially in nitrogen-containing compounds, leading to peaks at  $m/2$ . In the course of a common degradation process a  $\text{C}_3\text{H}_3^+$  fragment

is produced, for which a cyclopropenyl cation structure [1]<sup>18</sup> was proposed (McLafferty,<sup>15</sup> p. 138).

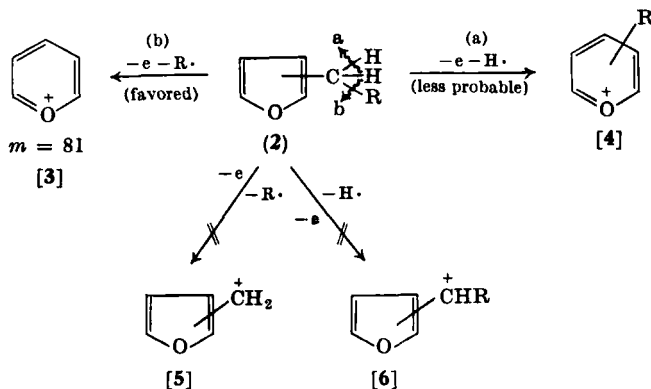
## A. OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

### 1. *Furans*

The spectrum of furan<sup>19</sup> shows, besides the molecular ion peak ( $M^+$ ), a very pronounced peak of the cyclopropenylium ion [1] at mass 39. This is in accordance with the rather low aromatic character of furan in comparison with other heterocyclics, facilitating its cleavage. Another fragment of higher intensity corresponds to the well-stabilized  $H-\overset{+}{C}=O$  ion of mass 29.

In monoalkyl-substituted furans (2) cleavage reactions in benzylic position are very favored. It is assumed that the resulting ion does not have structure [5] or [6] but rather exists in the ring-enlarged form [3]<sup>20</sup> or [4] by analogy with the mass spectrometric degradation of alkylbenzenes to tropylium ions<sup>21, 22</sup> which was proved unambiguously by labeling experiments. If the benzylic carbon is substituted, the loss of the substituent R is more favored than of  $H\cdot$ , because a  $C-C$  (or a  $C-O$ ) bond is weaker than a  $C-H$  bond, and also because the lone electron experiences more stabilization in  $R\cdot$  than in a hydrogen atom.

The common tendency to lose a substituent group more readily



<sup>18</sup> Ions and fragments are put in square brackets [ ], while molecules are symbolized by parentheses ( ).

<sup>19</sup> J. Collin, *Bull. Soc. Chim. Belges* **69**, 449 (1960).

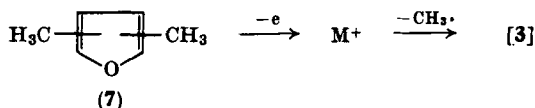
<sup>20</sup> J. Collin, *Bull. Soc. Chim. Belges* **69**, 575 (1960).

<sup>21</sup> S. Meyerson and P. N. Rylander, *J. Chem. Phys.* **27**, 901 (1957).

<sup>22</sup> P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Am. Chem. Soc.* **79**, 842 (1957).

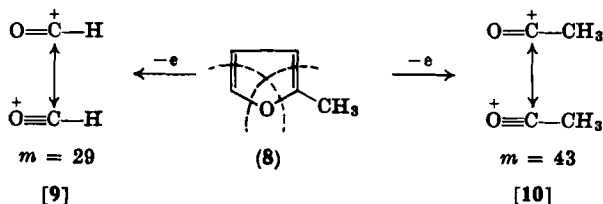
than a hydrogen atom is demonstrated by the spectra of furfuryl alcohol [(2), R=OH]<sup>20</sup> and furfuryl acetate (see Biemann,<sup>10</sup> p. 112) [(2), R=OCOCH<sub>3</sub>], where the peak corresponding to fragment [3] is much more pronounced than that of [4] (M-1).

The spectra of dimethyl-substituted furans<sup>19</sup> contain a rather strong peak at M-15, indicating the loss of a methyl group. Because the cleavage of a single bond in the neighborhood of a double bond is not favored for energetic reasons, it must be thought that the elimination of a methyl group proceeds during or after a rearrangement of the molecular ion of (7)→[3], again in agreement with the well-known behavior of analogous benzene derivatives.<sup>22a</sup>

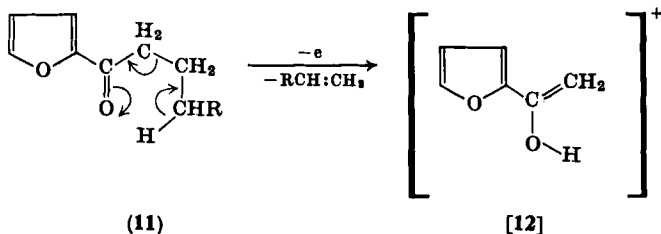


The presence of the methyl groups causes a shift of the cyclopropenyl ion [1] of unsubstituted furan by 14 mass units (MU), to mass 53, because in this case a methyleyclopropenyl cation is produced.

In  $\alpha$ -substituted monomethylfurans (8), formyl [9] and acetyl [10] ions are formed together:



Acyl-substituted furans of structure type (11)<sup>22b</sup> are cleaved preferentially in the course of a McLafferty rearrangement,<sup>23</sup> (11)→[12]:

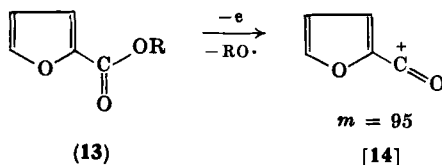


<sup>22a</sup> S. Meyerson and P. N. Rylander *J. Phys. Chem.* **62**, 2 (1958).

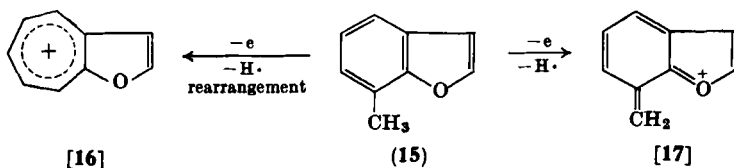
<sup>22b</sup> R. I. Reed and W. K. Reid, *J. Chem. Soc.* p. 5933 (1963).

<sup>23</sup> F. W. McLafferty, *Anal. Chem.* **31**, 82 (1959).

Furan carboxylic acids eliminate  $\text{CO}_2$  very readily.<sup>22b</sup> This reaction may be due partly to thermal cracking of the compounds prior to ionization.<sup>24</sup> In the corresponding esters the loss of the OR group is highly favored (Biemann,<sup>10</sup> p. 112)<sup>22b</sup> giving rise to a fragment of mass 95 in monocarboxylic esters, (13)→[14]:



Unsubstituted benzofuran and dibenzofuran show very intense peaks of the molecular ions,<sup>22b</sup> reflecting their high stability, caused by the lack of bonds which can be cleaved easily. The spectra of benzofurans substituted with a methyl group in the benzene ring (15) are characterized by abundant ions at M-1. They are assumed to have the oxonium ion structure [17] (see Budzikiewicz,<sup>11</sup> p. 230) rather than that of a tropylium ion [16],<sup>22b</sup> as might be supposed considering the decomposition of analogous benzene compounds.<sup>22b</sup>

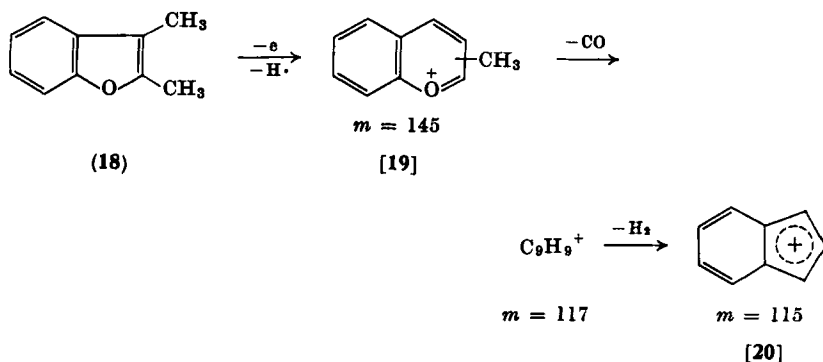


In this connection it should be mentioned that the spectrum indicates only mass numbers. From these mass numbers possible molecular and also structural formulas for the corresponding ions can be derived, and plausible degradation mechanisms are often postulated. It happens often that a degradation mechanism or a structural formula seems more plausible to one worker than to another. Therefore different mechanisms for similar reactions and also different structures for similar ions are sometimes proposed by different authors. For instance the M-1 ion in the spectrum of the methylbenzofuran (15) could have either structure [16] or [17]. In the degradation mechanisms

<sup>24</sup> N. S. Wulfson, V. J. Zaretsky, and V. G. Zaikin, *Izv. Akad. Nauk. SSSR* p. 2215 (1963); *Chem. Abstr.* **60**, 10040 (1964).

outlined in this chapter, we try to follow the principle that those decompositions most probably occur which are the most economical of energy.<sup>25</sup>

For alkylbenzofurans substituted in the furan ring, e.g., (18), cleavage with ring enlargement to a chromenyl ion is suggested,<sup>26</sup> (18)→[19]:



Further degradation leads, with expulsion of CO, to an ion  $C_9H_9^+$  which loses  $H_2$  to give a fragment of mass 115, thought to have the indenyl structure [20].

The main degradation path of 2-formylbenzofuran (21) is explained by loss of two molecules of CO, forming possibly a benzocyclopropene ion,<sup>26</sup> (21)→[22] [23], which can lose a hydrogen atom to give a fragment of mass 89, thought to be a dehydrotropylium ion [24], which is also found in the spectra of other benzofuran derivatives,<sup>22b</sup> coumarin,<sup>24</sup> and furanocoumarins.<sup>27, 28</sup>

Fragments of very low hydrogen content are also produced by the cleavage of dihydrobenzofuran-3-one.<sup>26</sup> Main fission reactions occur in this compound by loss of CHO or  $CH_2O$ , forming ions at M-29 and M-30. The latter fragment is reported to lose CO, producing an ion of mass 76, supposed to be a dehydrobenzene ion.

Nitrobenzofurans lose NO and  $NO_2$  very easily,<sup>22b</sup> typical behavior

<sup>25</sup> G. Spiteller and M. Spiteller-Friedmann, *Angew. Chem.* **77**, 393 (1965); *Internat. Ed. Engl.* **4**, 383 (1965).

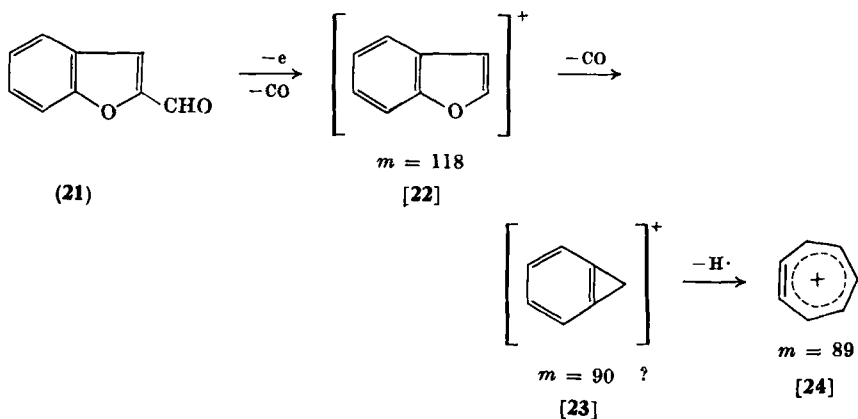
<sup>26</sup> B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron* **20**, 1185 (1964).

<sup>27</sup> C. S. Barnes and J. L. Occolowitz, *Australian J. Chem.* **17**, 975 (1964).

<sup>28</sup> N. S. Wulfson, V. J. Zaretsky, and V. G. Zaikin, *Dokl. Akad. Nauk SSSR* **155**, 1104 (1964); *Chem. Abstr.* **61**, 1737 (1964).



for otherwise aromatic nitro compounds.<sup>29</sup> After the elimination of NO the expulsion of CO gives rise to another prominent peak at M-58.<sup>22b</sup>



Acetamidobenzofurans are cleaved by loss of ketene,<sup>22b</sup> followed by elimination of CHO.

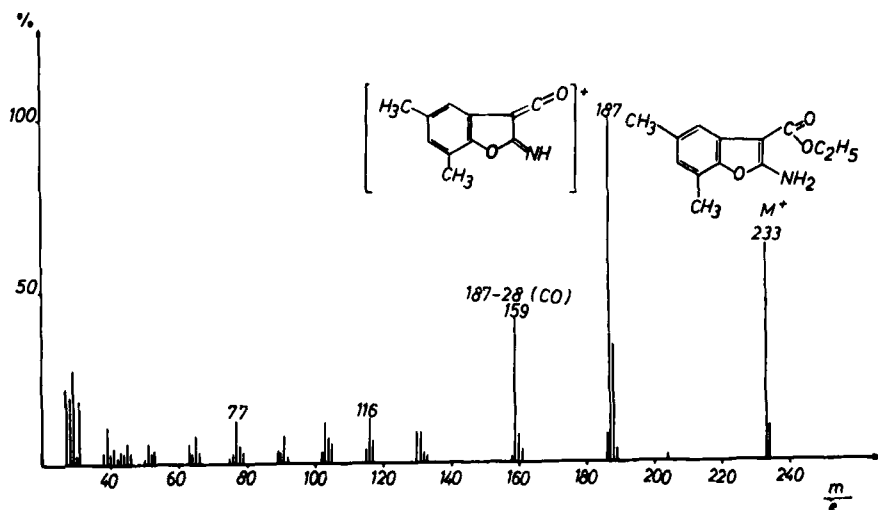
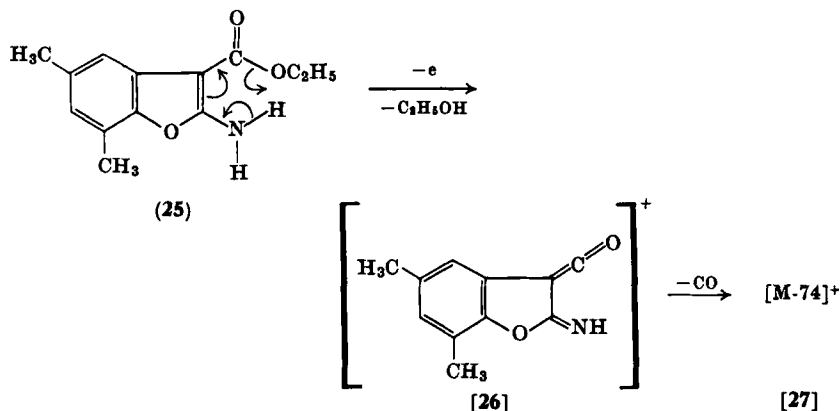


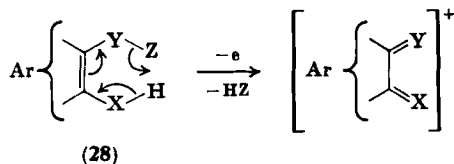
FIG. 1. Mass spectrum of the benzofuran derivative (25) [G. Spitteller, *Monatsh.* **92**, 1142 (1961)].

<sup>29</sup> J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belge* **29**, 311 (1964).

The *ortho* relationship of the amino group to the carbethoxy group in the benzofuran derivative (25) could be proved by mass spectrometry,<sup>30</sup> because the spectrum of the compound (Fig. 1) showed a strong "o effect"<sup>31, 32</sup> by loss of  $C_2H_5OH$  instead of  $C_2H_5O\cdot$ , a mechanism which is operative in aromatic compounds of the general formula (28). The resulting fragment [26] can then lose the stable CO molecule, (25)  $\rightarrow$  [26]  $\rightarrow$  [27]:



The fact that those mass spectrometric degradation reactions are favored for which the energy for the whole process is low is demonstrated again by the spectrum of difurylmethane (see Biemann,<sup>10</sup>



X = O, S, NH,  $CH_2$

Y =  $CH_2$ , CO

Z = OH, OR, SH, SR,  $NH_2$

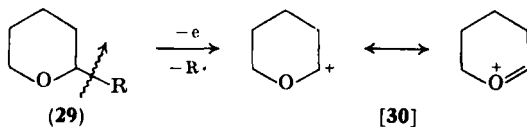
p. 139). This exhibits its strongest peaks at mass numbers which correspond to ions produced by the loss of a stable CO molecule and subsequent elimination of CHO, forming a tropylium ion. The gain of stabilization energy in the cleavage products obviously provides most of the energy for the fission reactions.

<sup>30</sup> G. Spiteller, *Monatsh.* **92**, 1142 (1961).

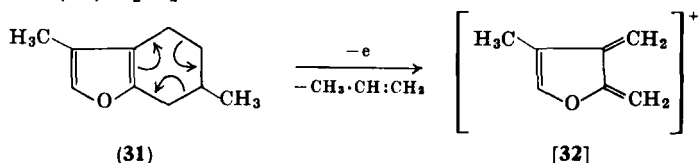
<sup>31</sup> F. W. McLafferty and R. S. Gohlke, *Anal. Chem.* **31**, 2076 (1959).

<sup>32</sup> G. Spiteller, *Monatsh.* **92**, 1147 (1961).

In  $\alpha$ -alkyl-substituted tetrahydrofurans and tetrahydropyrans<sup>26, 33, 34</sup> the elimination of the substituent is highly favored, because a resonance stabilized cation [30] is formed.

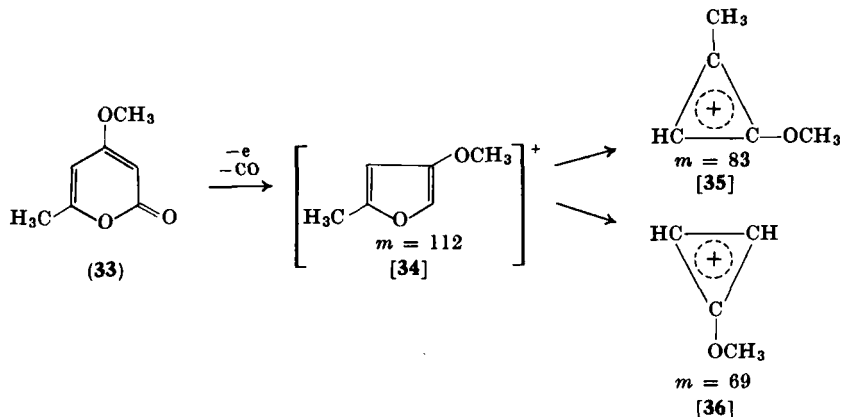


Tetrahydrobenzofurans (Biemann,<sup>10</sup> p. 106),<sup>26</sup> like compound (31) (Biemann, *loc. cit.*), are easily cleaved by a retro-Diels-Alder fission,<sup>35, 36</sup> (31)  $\rightarrow$  [32]:



## 2. Pyrones, Coumarins, and Chromans

Simple pyrones<sup>27, 37, 38</sup> (33)  $\rightarrow$  [34] are preferentially cleaved by loss of CO, forming the corresponding furan derivatives,<sup>37</sup> which



<sup>33</sup> C. F. Seidel, D. Felix, A. Eschenmoser, K. Biemann, E. Palluy, and M. Stoll, *Helv. Chim. Acta* **44**, 598 (1961).

<sup>34</sup> G. Ohloff, K. H. Schulte-Elte, and B. Willhalm, *Helv. Chim. Acta* **47**, 602 (1964).

<sup>35</sup> H. Budzikiewicz, J. I. Braumann, and C. Djerassi, *Tetrahedron* **21**, 1855 (1965).

<sup>36</sup> K. Biemann, *Angew. Chem.* **74**, 102 (1962); *Internat. Ed.* **1**, 98 (1962).

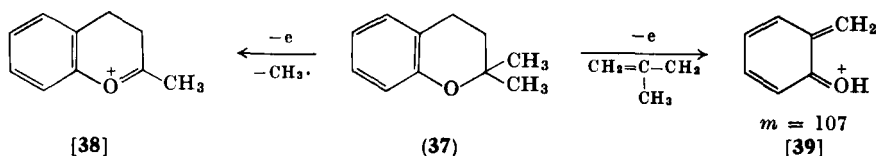
<sup>37</sup> H. Nakata, Y. Hirata, and A. Tatematsu, *Tetrahedron Letters*, p. 123 (1965).

<sup>38</sup> P. Break, T. H. Kinstle, and G. A. Carls, *J. Am. Chem. Soc.* **86**, 3833 (1964).

decompose further in the ways discussed above, e.g., [34]→[35], [34]→[36].

A similar degradation process is reported for coumarin<sup>24, 27</sup> and chromanones<sup>26</sup> which can lose one and two molecules of CO very easily.

Dimethylchromans,<sup>26, 27</sup> e.g., (37), are split by loss of a methyl group, (37)→[38], but a still more important fragment is produced in a reaction which was formulated as (37)→[39]<sup>26</sup>:



The behavior of more complicated oxygen-containing heterocyclic compounds under electron impact will be discussed in Section III, A.

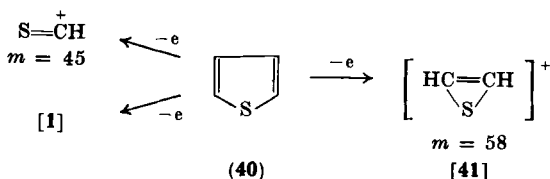
## B. SULFUR-CONTAINING HETEROCYCLIC COMPOUNDS

The natural isotope distribution of sulfur  $\text{S}^{32}:\text{S}^{34}$  is about 25:1. Therefore each peak in the mass spectrum of a sulfur compound which corresponds to a sulfur-containing fragment is accompanied by a second, shifted by 2 MU (mass units) to higher mass numbers. The intensity ratio of these two peaks depends upon the number of sulfur atoms present in the ion, if the contribution of other fragments to these peaks can be excluded: it is 25:1 if only one sulfur is present, 25:2 for two, and so on (Beynon,<sup>13</sup> p. 300). Therefore the presence of a sulfur-containing compound and the number of S atoms may be easily deduced from the ratio of the  $\text{M}^+$  and  $(\text{M} + 2)^+$  ions.

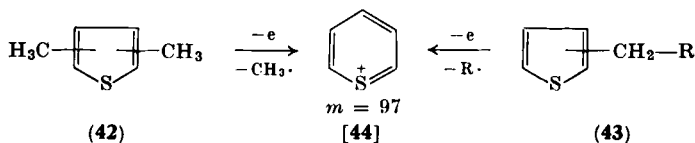
The main mass spectrometric degradation processes of thiophene and its derivatives are very similar to those of furan compounds. The higher atomic weight of sulfur (32) in comparison with oxygen (16) causes a shift of all hetero atom-containing fragments by 16 MU in thiophenes in comparison with the corresponding degradation products of furans. Thus, for example, the peak at mass 29 ( $\text{H}-\text{C}^+=\text{O}$ ) in the spectrum of furan is found at mass 45 ( $\text{H}-\text{C}^+=\text{S}$ ) in the spectrum of thiophene (Budzikiewicz,<sup>11</sup> p. 234).<sup>39</sup>

<sup>39</sup> V. Hanuš and V. Čermák, *Collection Czech. Chem. Commun.* **24**, 1602 (1959).

Sulfur shows a greater ability than oxygen to stabilize a positive charge. Therefore the hetero atom-containing fragments of sulfur compounds are produced with a greater probability than their oxygen analogs. For example, the intensity of the  $C_3H_3^+$  [1] peak in the spectrum of thiophene (40)<sup>39, 40</sup> is decreased in comparison with that of furan. For the same reason a strong peak at mass 58 [41] is observed in the spectrum of thiophene while the analogous ion of mass 42 from furan is produced only in low abundance



In alkylthiophenes<sup>39, 40</sup> [see Fig. 2, mass spectrum of  $\alpha$ -(*n*-butyl)-thiophene] cleavage reactions which proceed with ring enlargement are highly favored, (42)→[44], (43)→[44]:



The same characteristic behavior in alkylfurans has already been discussed. The tendency to fission of the benzylic bond in (43) becomes higher with an increasing number of carbon atoms in R. Therefore the intensity of the molecular ion peaks decreases very much in higher homologs (see Fig. 2). For alkylthiophenes with CH groups in the  $\beta$  position, a double rearrangement of hydrogen can occur, producing an ion of mass 85 from monoalkyl derivatives which are assumed to have the structure of a thiophenium cation (Budzikiewicz,<sup>11</sup> p. 234). The double rearrangement seems to be especially favored in *tert*-butyl-substituted thiophenes. The degradation reactions of benzothiophenes correspond to those of analogous furan derivatives (Budzikiewicz, *loc. cit.*, p. 235).

<sup>40</sup> I. W. Kinney, Jr. and G. L. Cook, *Anal. Chem.* **24**, 1391 (1952); **25**, 1729 (1953).

The high stability of aromatic systems causes, in the 1,2,3,4-tetrahydrodibenzothiophene (45), the otherwise unusual loss of four hydrogen atoms, (45)→[46] (Budzikiewicz, *loc. cit.*, p. 237), but the

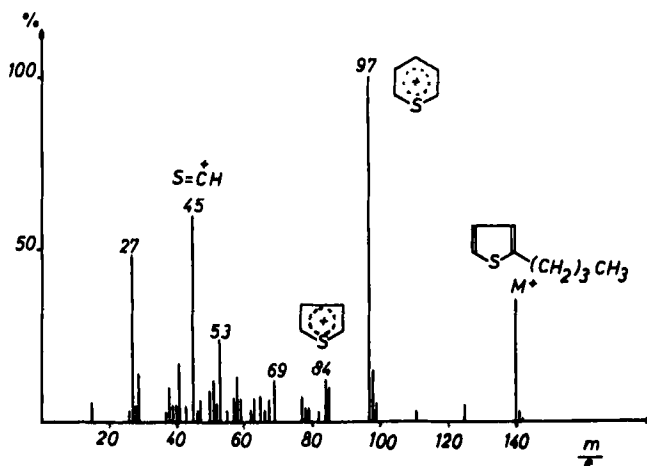
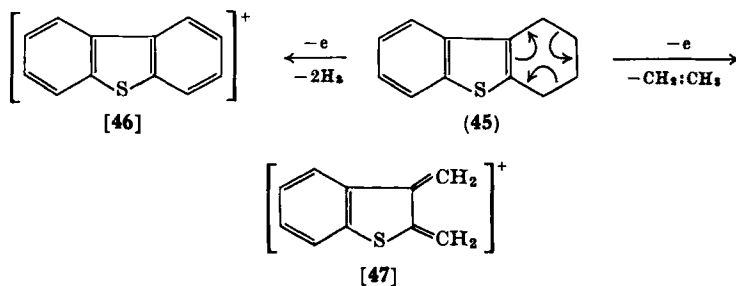


FIG. 2. Mass spectrum of  $\alpha$ -n-butylthiophene [V. Hanuš and V. Čermák, *Collection Czech. Chem. Commun.* **24**, 1802 (1959)]. (For better identification peaks below mass 97 are drawn by doubling their actual intensity.)

dominant fragmentation process in (45) is the elimination of a molecule of ethylene by a retro-Diels-Alder fission, (45)→[47]:



### C. NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

The even-numbered atomic weight of nitrogen and its uneven valence cause an uneven molecular weight of all compounds which contain an uneven number of nitrogens, while all other molecules

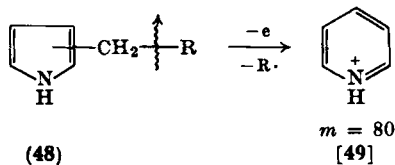
built up of C, H, O, S, and the halogens must always have an even-numbered molecular weight. So a nitrogen-containing compound is often recognizable by its molecular ion of uneven mass.

The spectra of unsubstituted nitrogen-containing heterocyclic compounds with an uneven number of nitrogens show the  $M^{++}$  ions at half mass numbers, which makes their detection very easy. Besides comparatively strong peaks for  $M^{++}$ , they are characterized by a strong tendency to eliminate one molecule of HCN.

### 1. Pyrroles

The mass spectra of pyrrole and its derivatives reveal that the main fission reactions are operative as in corresponding furans and thiophenes.<sup>41</sup> The spectrum of pyrrole shows the fragment analogous to the  $\text{H}-\overset{+}{\text{C}}=\text{O}$  ion of furan, i.e.,  $\text{H}-\overset{+}{\text{C}}=\text{N}-\text{H} \leftrightarrow \text{H}-\text{C}\equiv\overset{+}{\text{N}}-\text{H}$  at mass 28; the  $\text{C}_3\text{H}_3^+$  ion is also present and the ion corresponding to the fragment of mass 58 [41] in thiophene is now found at mass 41. A further fragment, characteristic of nitrogen-containing heterocyclics, is produced by loss of a HCN molecule. The molecular formulas of the different fragments were established unambiguously by high-resolution mass spectrometry.<sup>41</sup>

In  $\alpha$ -substituted methyl pyrroles the  $\alpha$  position of the substituent is indicated in the same manner as in furans and thiophenes by the fragment of mass 53 corresponding to the methyleyclopropenyl ion accompanying that of mass 39, the cyclopropenyl ion [1]. All alkylpyrroles have a strong tendency to form pyridinium ions by ring enlargement (48)  $\rightarrow$  [49]:

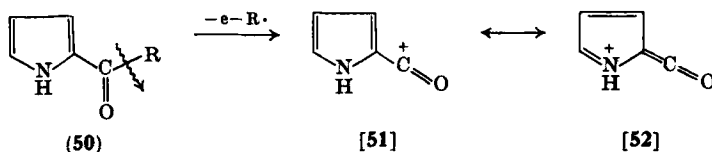


*N*-alkyl-pyrroles show different behavior: if the alkyl chain contains three or more carbons, a fragment of mass 81 is produced predominantly.<sup>41a</sup>

<sup>41</sup> H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, *J. Chem. Soc.* p. 1949 (1964).

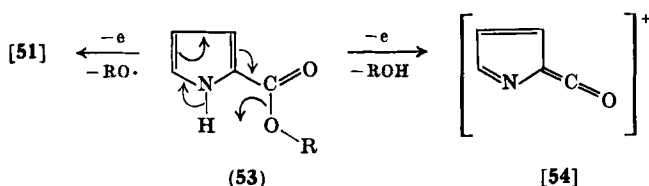
<sup>41a</sup> A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.* **87**, 805 (1965).

Acylpyrroles tend to lose the R substituent; the resulting ion from a 2-acylpyrrole can be formulated as [51]. (50)→[51]↔[52]<sup>41</sup>:



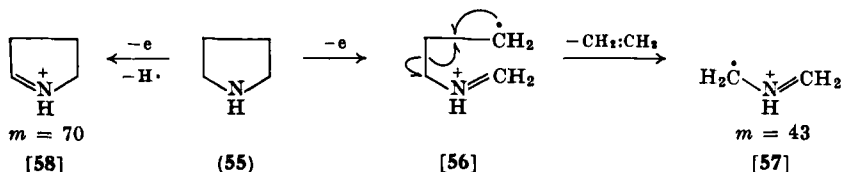
Facile loss of CO from the primary degradation product [51] is reported, but this does not occur in 3-acylpyrroles.<sup>41</sup>

As in the furan series, the loss of an  $\cdot\text{OH}$  or an  $\cdot\text{OR}$  group is very favored in pyrrole carboxylic acids and esters, (53)→[51]. The presence of an N—H group in  $\alpha$ -pyrrole carboxylic esters causes also the elimination of an ROH fragment,<sup>41</sup> (53)→[54].



A methyl substituent in an  $\alpha$ -position to a carboalkoxy group allows the operation of a McLafferty rearrangement as for the furan compound (see (25)→[26] and (28)).

The mass spectrum of pyrrolidine (55) contains the base peak (peak of highest intensity) at mass 43 (Budzikiewicz,<sup>11</sup> p. 98). This fragment is formed by cleavage of one C—C bond adjacent to the nitrogen with subsequent elimination of ethylene, (55)→[56]→[57]<sup>42</sup>:



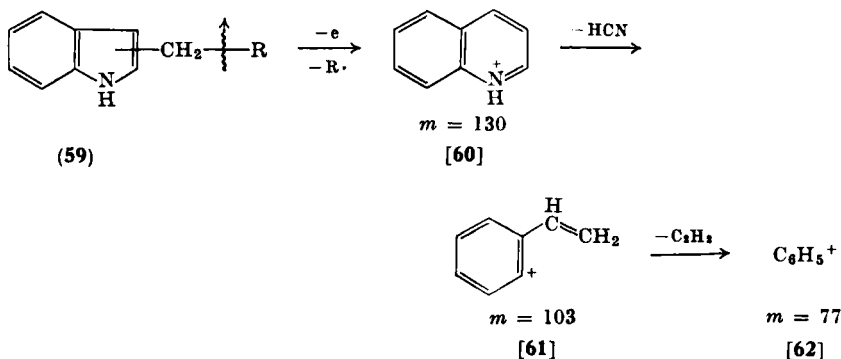
<sup>42</sup> Following a suggestion of Budzikiewicz, Djerassi, and Williams,<sup>11</sup> the shift of a lone electron is indicated as a fishhook  $\curvearrowright$  and that of an electron pair as an arrow  $\curvearrowleft$ , but in contrast to the cited authors we indicate the movement of each electron of a pair.



The loss of one H atom from an  $\alpha$ -carbon, (55)  $\rightarrow$  [58], is also highly favored.

## 2. Indoles

The mass spectra of indole and its alkyl derivatives reveal a close relationship to those of corresponding benzofurans and pyrroles (Beynon,<sup>13</sup> p. 397; Beynon and Williams<sup>43</sup>). A major degradation path is the formation of quinolinium ions, which may decompose further by expulsion of one molecule of HCN and one of acetylene, (59)  $\rightarrow$  [60]  $\rightarrow$  [61]  $\rightarrow$  [62]:



Esters of  $\alpha$ -benzindolecarboxylic acids are cleaved in the same manner as the corresponding esters of pyrrolecarboxylic acids.<sup>43a</sup>

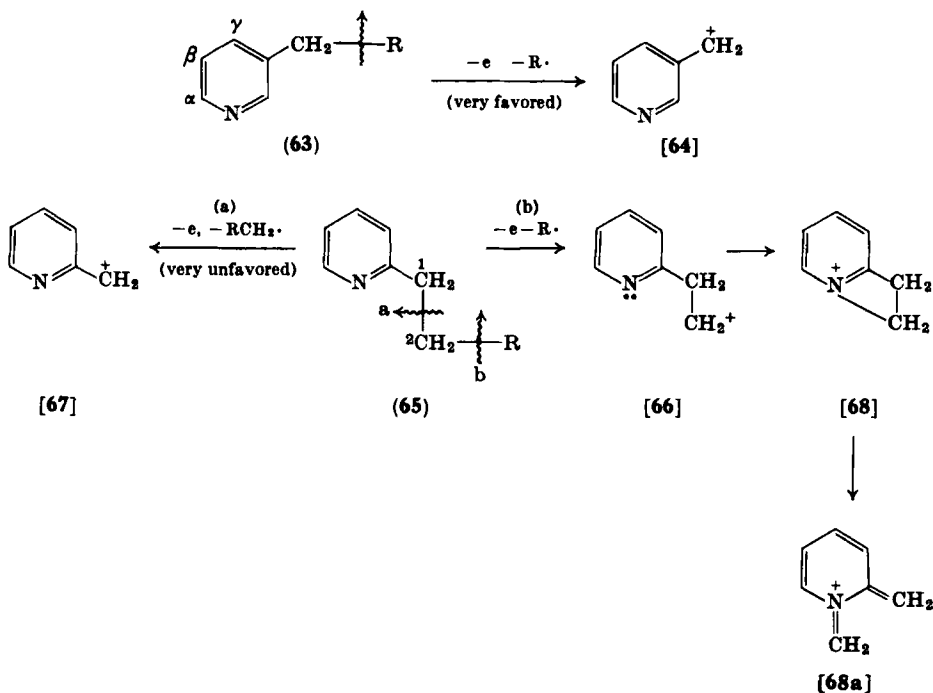
## 3. Pyridines

In alkyl-substituted five-membered heterocyclic compounds, the ring position of the alkyl substituent is only of minor influence on the degradation pattern; this can be understood by assuming ring enlargement to stable identical six-membered heterocyclic ions, regardless of the position of the alkyl substituent. The same observations were made by the examination of the spectra of alkylbenzenes, where *o*-, *m*-, and *p*-xylene, for example, show very similar spectra, caused by fact that they all are cleaved with formation of a tropylium ion; this was unambiguously proved by labeling experiments.

<sup>43</sup> J. H. Beynon and A. E. Williams, *Appl. Spectry*, **13**, 101 (1959); **14**, 27 (1960).

<sup>43a</sup> U. K. Pandit, H. J. Hofman, and H. O. Huisman, *Tetrahedron* **20**, 1679 (1964).

However the position of an alkyl substituent in pyridines is of great importance for the course of the main fission reactions,<sup>44</sup> suggesting that they do not give an identical ion (the azatropylium ion analogous to the tropylium ion).  $\beta$ -Alkylpyridines alone are cleaved preferentially by loss of an R substituent, (63)  $\rightarrow$  [64].  $\gamma$ -Substituted alkylpyridines show this cleavage reaction, but to a much lesser extent than do their  $\beta$ -substituted isomers<sup>44</sup> (Biemann,<sup>10</sup> p. 134).



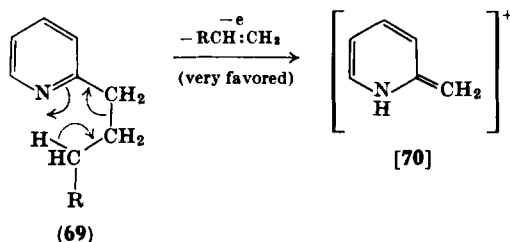
In contrast to  $\beta$ - and  $\gamma$ -alkyl-substituted pyridines, in their  $\alpha$  isomers (65), the rupture of a bond between C-2 and a hydrogen (as in the case of  $\alpha$ -ethylpyridine) or C-3 (as in the case of higher homologs), (65)  $\rightarrow$  [66], occurs with much higher probability than that between C-1 and C-2, (65)  $\rightarrow$  [67].

This characteristic behavior of the alkylpyridines substituted at different ring positions seems to indicate that the molecular ions are not involved in rearrangement processes prior to the cleavage of the

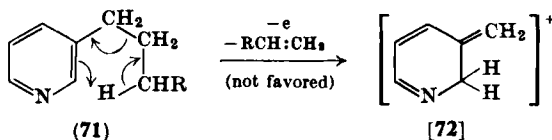
<sup>44</sup> K. Biemann and G. Spitteller, Unpublished work (see Biemann,<sup>10</sup> p. 134).

side chain. The preferred fission between carbon atoms 1 and 2 or 2 and 3 is explained by the positive charge being better stabilized in [64] than in [67]. This is because the pyridine nitrogen induces a positive charge at the  $\alpha$ -carbon atom, hindering the formation of a positive center at an adjacent carbon atom. This effect operates to a lesser extent in the  $\gamma$  position, and very little in the  $\beta$  position. The cleavage reaction (65)  $\rightarrow$  [66] may be explained by the positive charge at C-2 being stabilized by the lone electron pair of the nitrogen, forming a four-membered ring [68] which could be opened to the valence tautomere [68a].

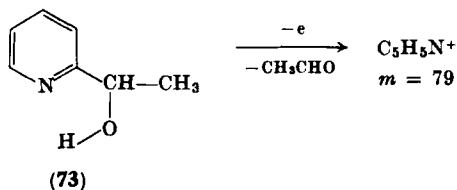
In  $\alpha$ -substituted alkylpyridines of type (69) a molecule of olefin is eliminated very easily, (69)  $\rightarrow$  [70]<sup>44</sup> (Biemann,<sup>10</sup> p. 130), by a McLafferty rearrangement:



If the hydrogen cannot shift to the nitrogen, as in the corresponding  $\beta$  or  $\gamma$  isomers, this rearrangement is only of minor importance, (71)  $\rightarrow$  [72] (Budzikiewicz,<sup>11</sup> p. 255):



Pyridines with a  $C_2$  side chain in the  $\alpha$  position readily lose the side chain with a hydrogen shift to the nucleus. Thus, for example,



$\alpha$ -ethylpyridine eliminates ethylene,  $\alpha$ -vinylpyridine acetylene,  $\alpha$ -acetylpyridine ketene, and  $\alpha$ -1-hydroxyethylpyridine (73) loses acetaldehyde. The mechanisms of these reactions are not yet clarified.

In  $\alpha$ -hydroxypyridine (Fig. 3), which exists mainly in the pyridone structure, the elimination of CO is the predominating cleavage re-

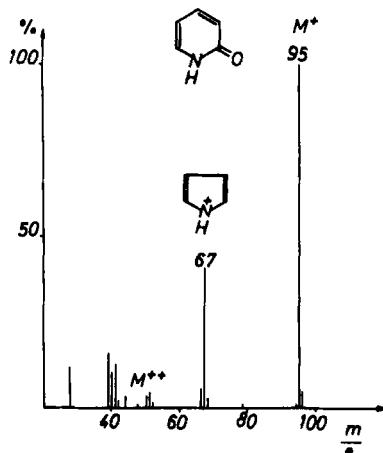
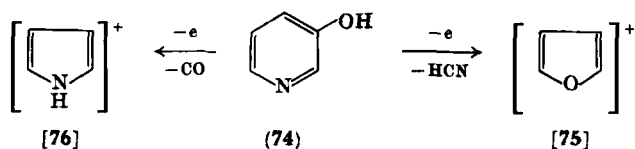
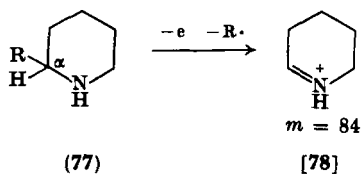


FIG. 3. Mass spectrum of  $\alpha$ -pyridone [G. Spitteller and M. Spitteller-Friedmann, *Monatsh.* **93**, 1395 (1962)].

action, while in  $\beta$ -hydroxypyridine, which cannot exist as a pyridone, the expulsion of HCN is as likely as that of CO,<sup>45</sup> (74)  $\rightarrow$  [75], (74)  $\rightarrow$  [76]:



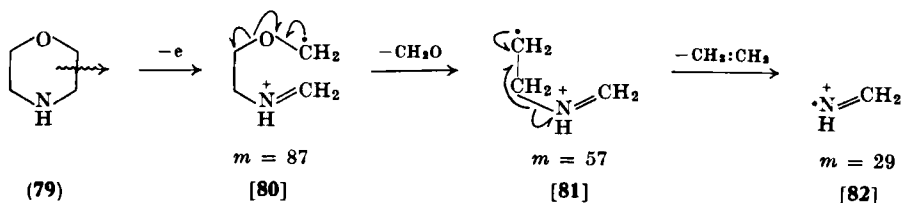
From piperidine ( $R=H$ ) (77) and its  $\alpha$ -substituted monoalkyl



<sup>45</sup> G. Spitteller and M. Spitteller-Friedmann, *Monatsh.* **93**, 1395 (1962).

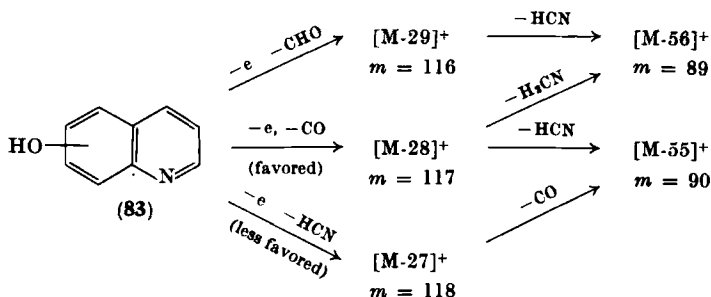
derivatives ( $R = \text{alkyl}$ ) a highly stabilized particle could be obtained by the loss of a hydrogen atom (or the substituent  $R\cdot$ ), forming a prominent ion of mass 84 [78] (see Budzikiewicz,<sup>11</sup> p. 100).<sup>46, 47</sup>

Morpholine (79) is cleaved first at a C—C bond, followed by decomposition of the primary degradation product [80] by expulsion of formaldehyde (Beynon,<sup>13</sup> p. 394), (79)→[80]→[81]→[82]:



#### 4. Quinolines and Isoquinolines

There are only a few mass spectra of simple quinolines and isoquinolines reported in the literature.<sup>48</sup> The unsubstituted quinoline



and isoquinoline molecules are very stable but can lose HCN. The higher stability of the pyridine ring in quinolines which are substituted with a OH group in the benzene ring (83) is reflected by their greater

<sup>46</sup> A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.* **87**, 810 (1965).

<sup>47</sup> R. A. Saunders and A. E. Williams, *Conf. Mass Spectrometry, Paris, 1964*; to be published in "Advances in Mass Spectrometry", Vol. 3, Pergamon Press, Oxford.

<sup>48</sup> "Catalog of Mass Spectral Data," Manufacturing Chemists Assoc. *Res. Project No. 44*. Carnegie Inst. Technol., Pittsburg, Pennsylvania.

inclination to eliminate a molecule of CO or CHO than one of HCN. The further degradation of such compounds proceeds with loss of HCN and  $\text{H}_2\text{CN}$ , producing a characteristic double peak at mass 89 (dehydrotropylum ion [24]) and 90.<sup>49</sup>

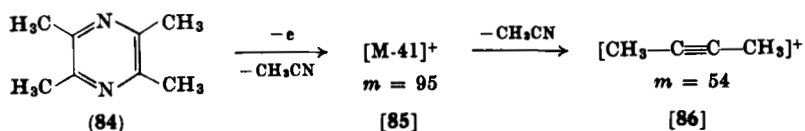
In isoquinolines substituted with an amino group in the benzene ring a similar degradation pattern is observed: loss of HCN [instead of CO as in compound (83)] and  $\text{H}_2\text{CN}$  (instead of HCO) gives important fragments. Their further decomposition is possible by ejection of either  $\text{H}_2\text{CN}$  or HCN,<sup>49</sup> again forming ions of mass 89 and 90.

### 5. Pyrazines

The mass spectrometric behavior of alkylated pyrazines resembles that of  $\alpha$ -alkyl-substituted pyridines, which also have the side chain attached to a ring carbon adjacent to a nitrogen (Biemann,<sup>10</sup> pp. 184, 132; Biemann in<sup>12</sup>, p. 534). A prominent cleavage reaction in such compounds occurs at a C-2—C-3 bond in the side chain (cf. (65)→[66]), probably because the positive charge at C-2 of the chain is stabilized in the same manner as in [68a].

If the side chain is long enough for a McLafferty rearrangement this is the predominant cleavage process (cf. the  $\alpha$ -alkylpyridines, (69)→[70]).

In tetramethylpyrazine (84) the main fission ruptures the ring system with successive loss of two molecules of acetonitrile, finally forming dimethylacetylene, (84)→[85]→[86] (Budzikiewicz,<sup>11</sup> p. 259):



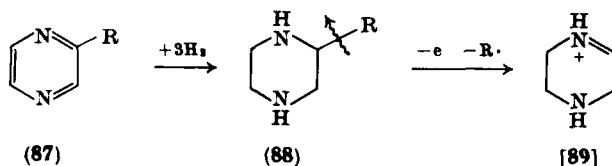
Acylpyrazines lose the acyl substituent as ketene in a manner similar to  $\alpha$ -acylpyridines<sup>50</sup> [compare the degradation of 1-hydroxyethylpyridine (73)].

Alkylpiperazines are easily cleaved by elimination of the substituent R (Biemann, *loc. cit.*). Therefore the length of the side chain in pyrazines may be determined by their reduction to the correspond-

<sup>49</sup> G. Spiteller and M. Spiteller-Friedmann, Unpublished work.

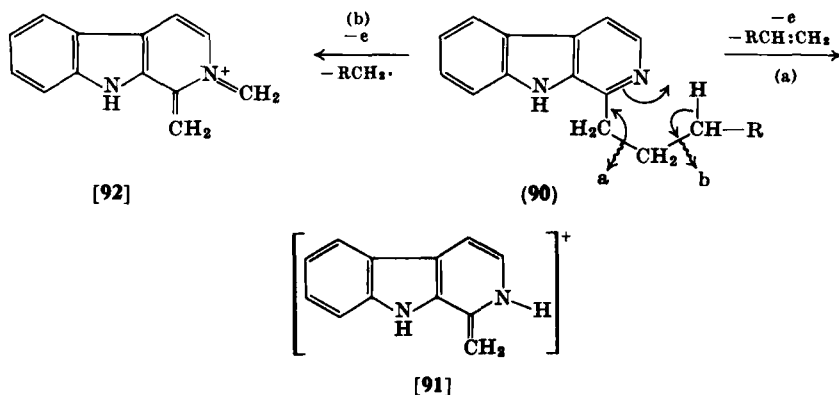
<sup>50</sup> B. Willhalm, *Joint Meeting Swiss Austrian Chem. Soc., Innsbruck, 1963*.

ing piperazines, (Biemann, *loc. cit.*; Biemann in<sup>12</sup>, p. 535) (87)→(88)→[89]:



### 6. $\beta$ -Carbolines

The mass spectra of only a few 1-alkyl-substituted  $\beta$ -carbolines have been investigated (Biemann, *loc. cit.*, p. 302). If the side chain is longer than two carbon atoms, the McLafferty rearrangement is the most important degradation process, as for the appropriately substituted  $\alpha$ -alkylpyridines and alkylpiperazines, (90)→[91]. If the first

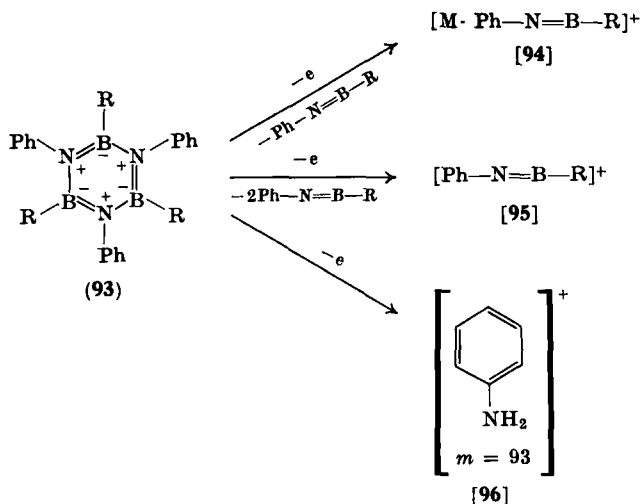


carbon of the side chain is not substituted, the fission of the bond between the second and third carbon (b) is more favored than that between the first and second (a), also in accordance with the behavior reported from  $\alpha$ -alkylpyridines and  $\alpha$ -alkylpiperazines, (90)→[92].

### D. BORAZOLES

The spectra of tri-*N*-phenylborazoles (93) are characterized by fragments which are produced by the loss of one or two molecules of  $Ph-N=B-R$  from the molecular ion. Besides this, an ion of mass

93, probably having the structure of an aniline cation radical, is very typical,<sup>51</sup> (93)→[94], (93)→[95], (93)→[96]:



### III. Special Groups of Heterocyclic Compounds

Only a very small number of different classes of more complicated heterocyclic compounds, mainly natural products, have so far been investigated by mass spectrometry. These compounds often have the same skeleton and differ one from another only by the presence of one or more substituents. If these substituents do not influence the fragmentation to a great extent, the mass spectra are similar except that those fragments which contain the substituents are correspondingly shifted. Therefore it is necessary only to discuss the spectrum of a typical representative of each class of compound and to give an explanation for the production of those fragments which show the characteristic features of the investigated class in order to obtain a key to the structure determination of further members of the class. Naturally the presence of one such key fragment alone is not evidence enough to postulate the existence of a certain group, because fragments of different structure may have the same mass number, but, by combining the inferences drawn from the presence of different key fragments with chemical experiments, the probable identification of structural features in unknown compounds may be achieved.

<sup>51</sup> W. Snedden, in "Advances in Mass Spectrometry" (R. M. Elliot, ed.), p. 456. Pergamon Press, Oxford, 1963.



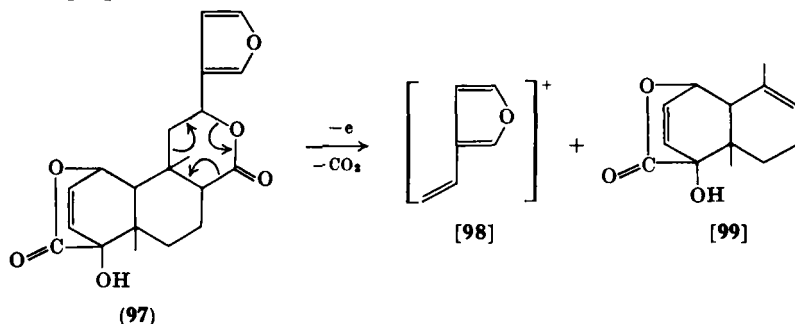
To give a short survey of the characteristic fragmentation patterns of the compounds discussed, the reproduced spectra contain only the key fragments; the minor peaks necessary for their identification may be found in the literature.

### A. OXYGEN-CONTAINING COMPOUNDS

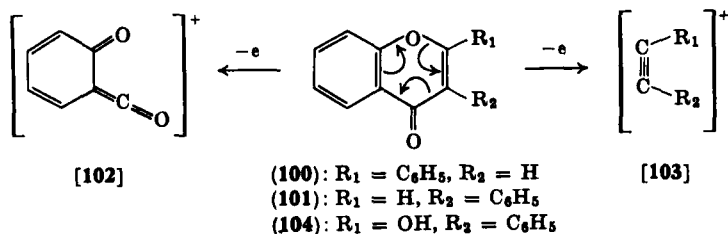
#### 1. Naturally Occurring Furan Derivatives

The mass spectra of naturally occurring oxygen heterocyclics were reviewed only recently.<sup>52</sup>

The mass spectra of columbin (**97**) and some closely related compounds have been published and discussed.<sup>22b</sup> The most prominent cleavage reaction possibly involves a cyclic mechanism in which one molecule of CO<sub>2</sub> is eliminated and a stable vinylfuran ion is produced, (**97**)→[**98**]:



hydroxy substituents give rise to peaks at M-15, M-28, and M-(28 + 15), indicating the elimination of a  $\text{CH}_3\cdot$  or CO group or both.<sup>53,53a</sup>



A main cleavage reaction is a retro-Diels-Alder fission, (100)→[102], (100)→[103], (101)→[102], (101)→[103]. The positive charge can be situated on both possible fragments.<sup>53</sup> By a concomitant hydrogen shift an important fragment 1 MU heavier than [102] is produced. The typical fragmentation behavior contributed very much to the structural elucidation of robustic acid<sup>54</sup> and scanenine,<sup>55</sup> containing the structure elements (104).<sup>55a</sup>

Mass spectrometry was also helpful in determining the structure of the isoflavone derivative munetone.<sup>56</sup>

The retro-Diels-Alder fission becomes very important in dihydroflavones and dihydroisoflavones; the charge is mainly localized in the dihydro derivative of [103]. Such compounds therefore exhibit very characteristic spectra.

The same cleavage reaction occurs in rotenoids containing the chromanochromanone system (105).<sup>53,57</sup> From the primary fission product of the retro-Diels-Alder decomposition [107], containing rings A and B, a highly stabilized aromatic system is formed by loss of a hydrogen atom, (105)→[107]→[108].

The presence of additional methoxyl groups as in sermudone (106) (Fig. 4) causes some further degradation reactions of the primary

<sup>53</sup> R. I. Reed and J. M. Wilson, *J. Chem. Soc.* p. 5949 (1963).

<sup>53a</sup> A. Pelter, P. Stainton, and M. Barber, *J. Heterocyclic Chem.* **2**, 262 (1965).

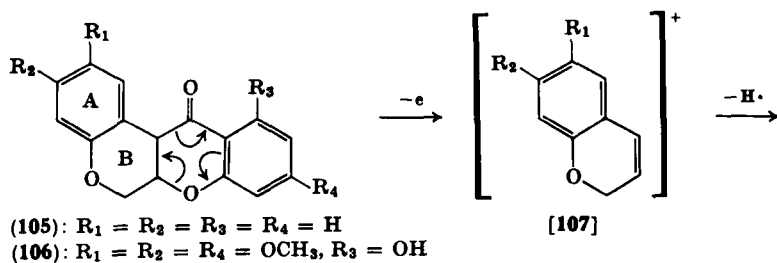
<sup>54</sup> A. P. Johnson, A. Pelter, and M. Barber, *Tetrahedron Letters*, p. 1267 (1964).

<sup>55</sup> A. Pelter and P. Stainton, *Tetrahedron Letters*, p. 1209 (1964).

<sup>55a</sup> A. Pelter, P. Stainton, A. P. Johnson, and M. Barber, *J. Heterocyclic Chem.* **2**, 256 (1965).

<sup>56</sup> C. S. Barnes, J. L. Occolowitz, N. L. Dutta, P. M. Nair, P. S. Phadke, and K. Venkataraman, *Tetrahedron Letters*, p. 281 (1963).

<sup>57</sup> R. I. Reed, W. K. Reid, and J. M. Wilson, in "Advances in Mass Spectrometry" (R. M. Elliot, ed.), p. 416. Pergamon Press, Oxford, 1963.



fragments, involving loss of the functional groups as  $CH_2O$ ,  $CH_3\cdot$ , and  $CO$ , but they are only of minor importance.

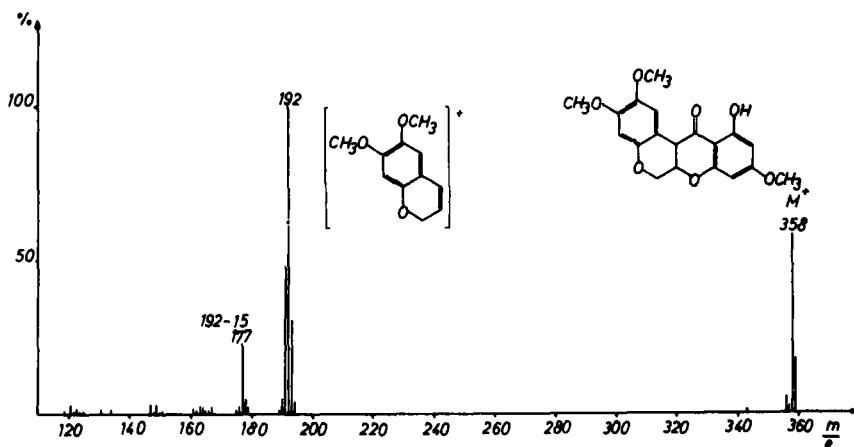
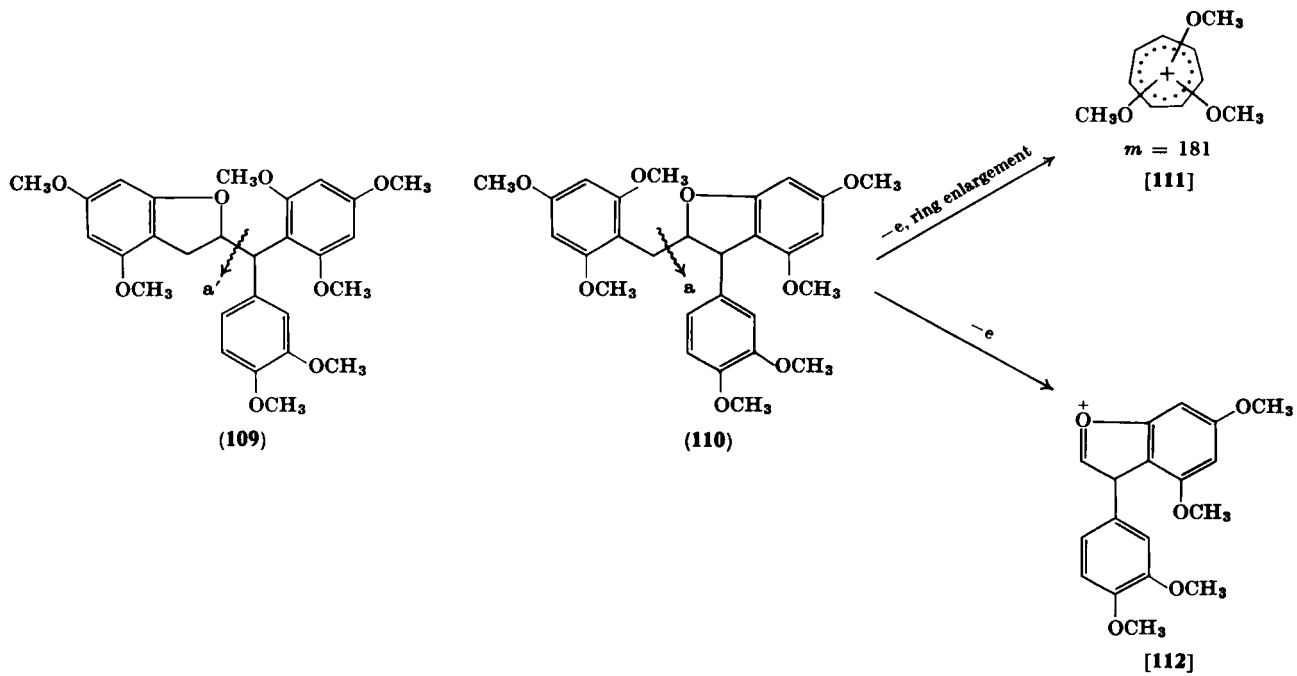


FIG. 4. Mass spectrum of sermudone [R. I. Reed and J. M. Wilson, *J. Chem. Soc. p. 5949* (1963)].

### 3. Benzodihydrofuran Compounds and Tetrahydrofuran Derivatives

Alternative structures (109) and (110) were proposed for the methylated product of the acid-catalyzed condensation of catechin



with phloroglucinol. Mass spectrometry differentiated these two. The only main fragments at mass 181 and 315 were ascribed structures [111] and [112], proving formula (110). Similar cleavage of bond a' in (109) would produce different fragments as shown by the investigation of model compounds.<sup>58</sup>

The typical cleavage reactions of  $\alpha$ -substituted tetrahydrofuran derivatives made possible the structural elucidation of a degradation product obtained from the mold metabolite erythroskyrine<sup>59</sup> and a complicated bistetrahydrofuran compound produced by isomerization of farnesol diepoxide.<sup>34</sup>

## B. NITROGEN-CONTAINING COMPOUNDS

### 1. *Alkaloids*

Mass spectrometry has been very successfully applied to alkaloids, especially those of the indole and indoline series. Even complicated alkaloids frequently give simple spectra with significant key fragments; sometimes this permits structure determination with only a minute amount of sample. The occurrence of a great number of alkaloids having the same skeleton, and differing only in the substituents, makes the comparison technique, briefly mentioned in the introduction to Section III, extremely useful. Since its first application in alkaloid chemistry in 1960 by Biemann,<sup>60</sup> the structures of nearly a hundred unknown alkaloids have been elucidated with the aid of mass spectrometry. A comprehensive review on the mass spectra of alkaloids can be found in the book of Budzikiewicz, Djerassi, and Williams.<sup>61</sup>

a. *Tropane Alkaloids*. Tropanol (113), and especially its acyl derivatives, are readily cleaved at the bond between C-3 and the oxygen. In the resulting ion there is thought to be some stabilization by the lone electron pair at the nitrogen, forming two four-membered

<sup>58</sup> W. Mayer, F. Merger, G. Frank, K. Heyns, and H. F. Grützmacher, *Naturwiss.* **50**, 153 (1963); K. Heyns, H. F. Grützmacher, W. Meyer, F. Merger, and G. Frank, *Liebigs Ann. Chem.* **675**, 134 (1965).

<sup>59</sup> J. Shoji and S. Shibata, *Chem. Ind. (London)*, p. 419 (1964).

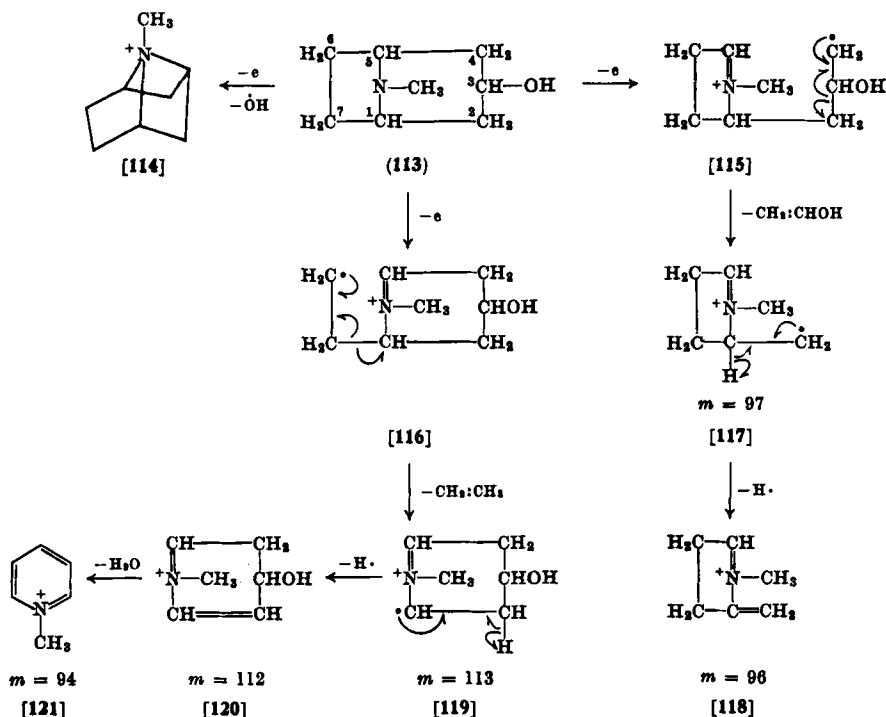
<sup>60</sup> K. Biemann, *Tetrahedron Letters* **15**, 9 (1960).

<sup>61</sup> H. Budzikiewicz, C. Djerassi, and D. H. Williams, in "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, "Alkaloids," Holden Day, San Francisco, 1964.

rings [114]. As usual the rupture of C—C bonds adjacent to the nitrogen is favored, (113)→[115], (113)→[116].<sup>62, 63</sup>

The primary decomposition product [115] is assumed to lose vinyl alcohol and a hydrogen atom to give a key fragment of mass 96, [115]→[117]→[118].<sup>62</sup>

Another degradation path involves the elimination of ethylene from the intermediate [116], [116]→[119]. The ion of mass 113 [119]



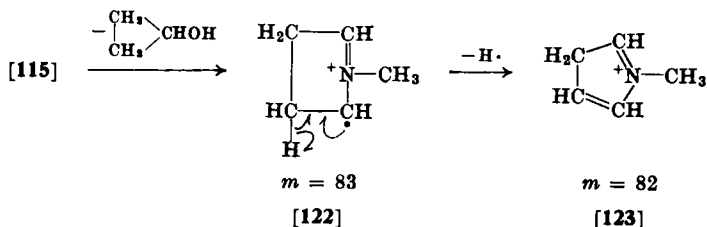
is stabilized by expulsion of a hydrogen atom and a molecule of water, forming the methylpyridinium ion, [119]→[120]→[121].

Cleavage of the primary decomposition product [115] with loss of cyclopropanol yields an ion of mass 83, which is stabilized by elimination of a hydrogen atom, [115]→[122]→[123].

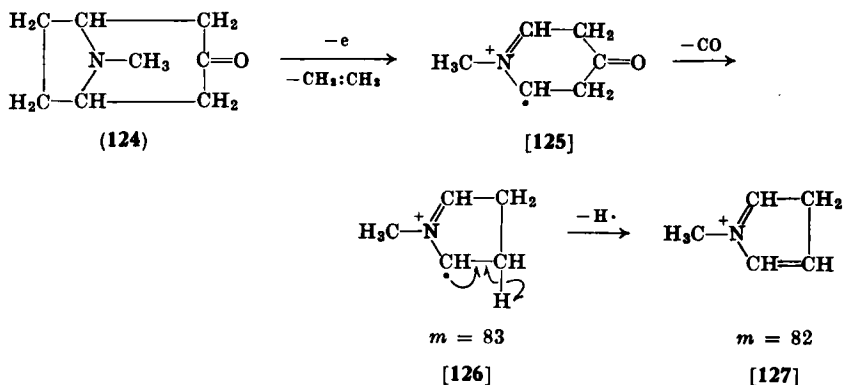
<sup>62</sup> J. Parelo, P. Longevialle, W. Vetter, and J. A. McCloskey, *Bull. Soc. Chim. France* p. 2787 (1963).

<sup>63</sup> E. C. Blosssey, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron* **20**, 585 (1964).

The tropanol fragmentation pattern was very useful in establishing the structure of the alkaloid phyllalbine.<sup>62</sup>



The process (113)→[116]→[119] becomes very important in tropanone (124). The intermediate [125] easily loses CO and a hydrogen atom, producing another ion of mass 82, this time assumed to come from the piperidine moiety, [125]→[126]→[127]. Therefore peaks at mass 82 and 83 do not necessarily give evidence for the presence of an *N*-methylpyrrolidine system. An alternative route, involving a McLafferty rearrangement for the production of the fragment of mass 82, was also discussed.<sup>63</sup>

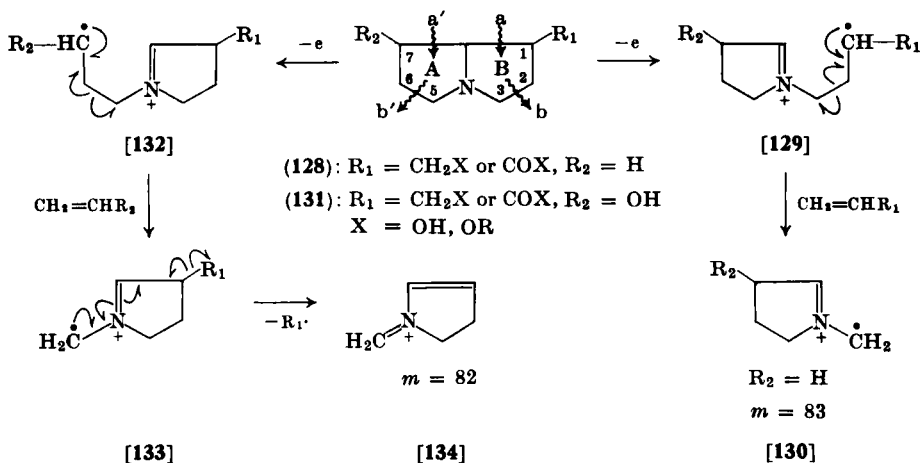


b. *Pyrrolizidine Alkaloids*. The fragmentation pattern of pyrrolizidine alkaloids<sup>64, 65</sup> is highly characteristic, depending on the presence of substituents at carbons 1 and 7<sup>64</sup> and a double bond in position 1, 2.

<sup>64</sup> N. Neuner-Jehle, H. Nesvadba, and G. Spiteller, *Monatsh.* **96**, 321 (1965).

<sup>65</sup> C. C. J. Culvenor, J. D. Morrison, A. J. C. Nicholson, and L. W. Smith, *Australian J. Chem.* **16**, 131 (1963).

Pyrrolizidine alkaloids with no oxygen function in 7 (**128**) are cleaved at bonds a and b, losing an ethylene derivative, (**128**)→[**129**]→[**130**].



If an additional OH function is present in position 7 (**131**) fission of bond a' and b' dominates, followed by elimination of the substituent at position 1, (**131**)→[**132**]→[**133**]→[**134**]. A double bond in position 1,2 suppresses cleavage of ring B. The pattern was shown to be drastically changed by the presence of an ester function, thus enabling the structural determination of unknowns.<sup>64</sup>

Rather similar degradation processes are reported for the indolizidine alkaloid securinine.<sup>66</sup>

c. *Pyridine- and Piperidine-type Alkaloids.* Nicotine (**135**) and its relatives<sup>67</sup> show in their mass spectra characteristic peaks corresponding to the pyrrolidine (nicotine) or piperidine (anabasine) part of the molecule. They are obviously produced by fission of the bond connecting the pyridine with the pyrrolidine or piperidine moiety, although the rupture of a bond adjacent to an aromatic system is not usually favored, (**135**)→[**136**]. This indicates the high stabilization of a positive charge by the tertiary aliphatic  $\text{N}_b$ , even more than that by an aromatic system.

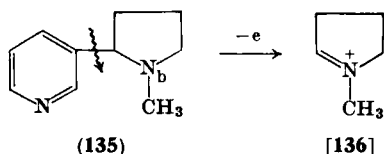
In the mass spectrum of nornicotine<sup>67</sup> the peak corresponding to ion [**136**] at mass 70 is of much lower intensity, because the lack of the

<sup>66</sup> J. Parello, A. Melera, and R. Goutarel, *Bull. Soc. Chim. France* p. 898 (1963).

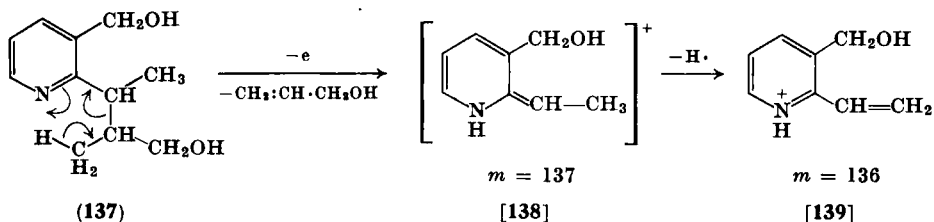
<sup>67</sup> A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.* **87**, 2926 (1965).



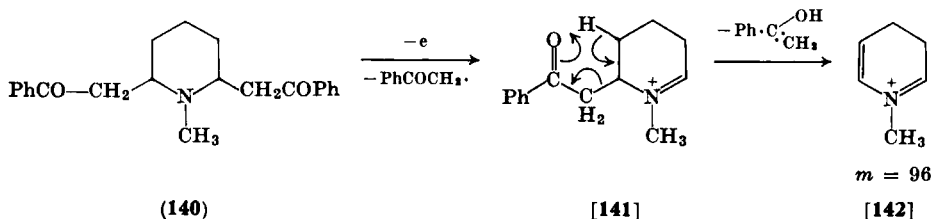
$N_b$ -methyl group diminishes the electron density at  $N_b$  and therefore its ability to stabilize a positive charge at an adjacent carbon.



The molecular weight of evonine,<sup>68</sup> composed of a base and a polyhydroxy moiety of still unknown structure, could not be determined by mass spectrometry, because the alcohol component was too easily eliminated. Nevertheless, important parts of the structure of the base can be deduced from the mass spectrum of the  $LiAlH_4$ -reduction product of evonine (137) which exhibits a significant peak at mass 137, indicating the presence of a substituted pyridine of type [138], (137)  $\rightarrow$  [138]  $\rightarrow$  [139]:



Lobelia alkaloids, e.g., lobelanine (140), can easily lose one of the side chains. The primary degradation product [141] is further cleaved by a McLafferty rearrangement to [142]. Other key fragments corre-



spond to the benzoyl ion and the phenyl ion produced from the former by expulsion of  $CO$ <sup>69</sup> (see Fig. 5).

<sup>68</sup> M. Pailer and R. Libiseller, *Monatsh.* **93**, 511 (1962).

<sup>69</sup> M. Spiteller-Friedmann and G. Spiteller, *Monatsh.* **96**, 104 (1965).

The dimeric structure of carpaine<sup>70</sup> and pseudocarpaine<sup>70a</sup> was elucidated by mass spectrometry.

The fragmentation pattern of piperidine alkaloids substituted in positions 3 and 4 is much more complicated (see Budzikiewicz *et al.*,<sup>61</sup> p. 225).<sup>71</sup>

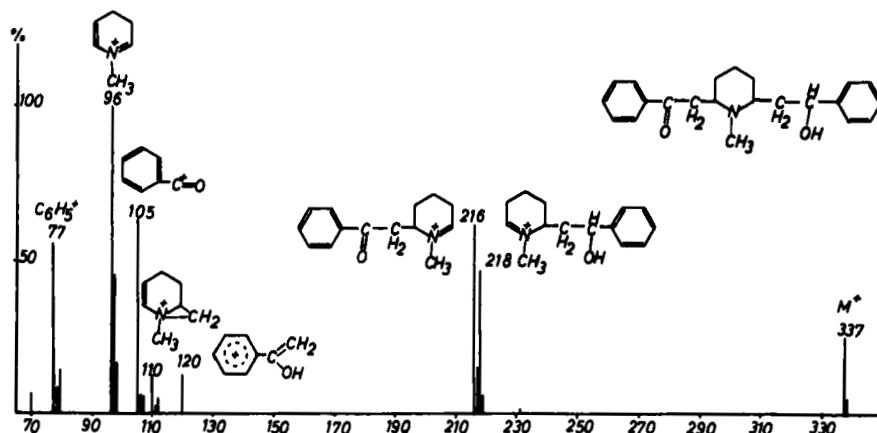


FIG. 5. Mass spectrum of lobeline [M. Spitteller-Friedmann and G. Spitteller, *Monatsh.* **96**, 104 (1965)].

d. *Quinolizidine Alkaloids.* The main fission in lupinine (**143**) and related alkaloids<sup>72</sup> occurs at bond a. The primary degradation product [**144**] can lose one molecule of allyl alcohol, [**144**] $\rightarrow$ [**145**]. The resulting ion [**145**] is stabilized by elimination either of a hydrogen atom or of ethylene, [**145**] $\rightarrow$ [**146**], [**145**] $\rightarrow$ [**147**]:

Another typical fission proceeds with loss of cyclopropylcarbinol or  $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{OH}$  from the primary degradation product [**144**], forming a fragment of mass 97.

The presence of a furan substituent at C-4, as in nupharidine (**148**), changes the fragmentation behavior drastically. The main fragments<sup>73</sup>

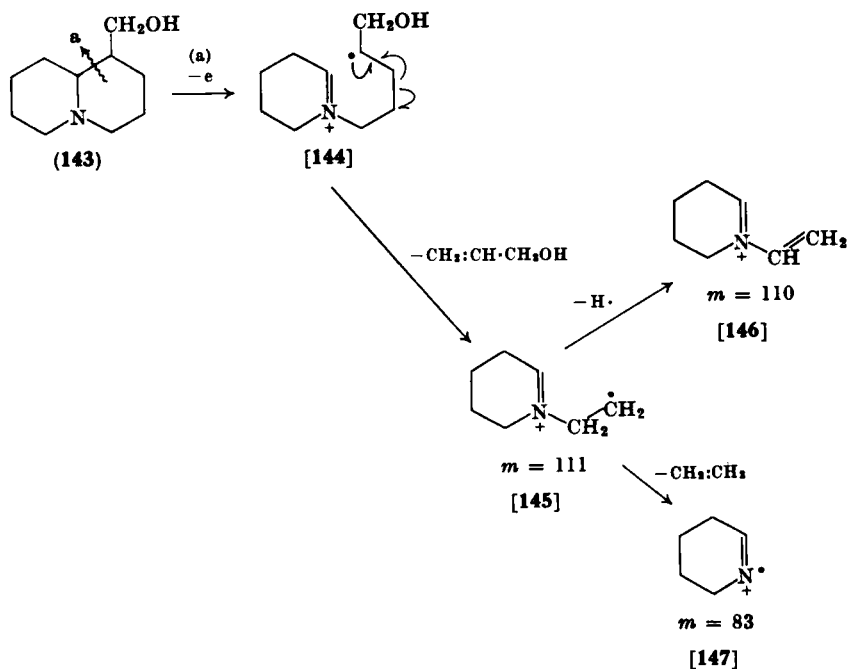
<sup>70</sup> M. Spitteller-Friedmann and G. Spitteller, *Monatsh.* **95**, 1234 (1964).

<sup>70a</sup> T. R. Govindachari, K. Nagarajan, and N. Viswanathan, *Tetrahedron Letters* p. 1907 (1965).

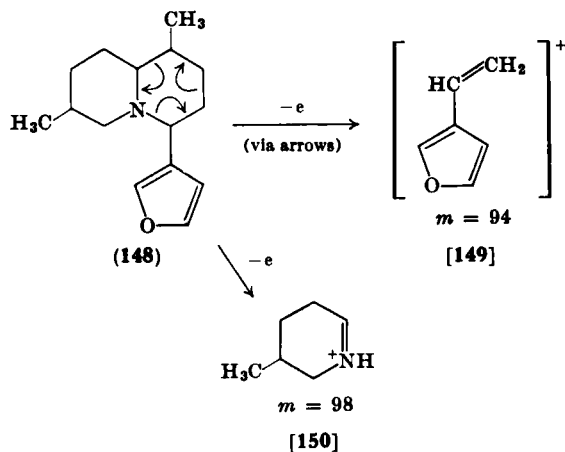
<sup>71</sup> Y. Hammonds, M. Plat, and J. LeMen, *Bull. Soc. Chim. France*, 2802 (1963).

<sup>72</sup> N. Neuner-Jehle, H. Nesvadba, and G. Spitteller, *Monatsh.* **95**, 687 (1964).

<sup>73</sup> O. Achmatowicz, H. Banaszek, G. Spitteller, and J. T. Wróbel, *Tetrahedron Letters* p. 927 (1964).



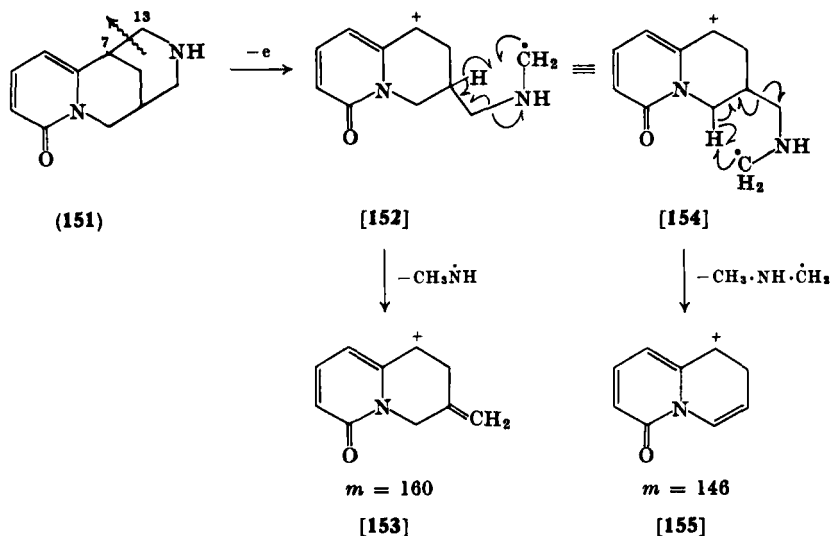
are now found at mass 94 and 98, corresponding to the stable ions [149] and [150].



By comparison of the mass spectra of nupharidine and thiobinupharidine, together with chemical degradation work and other

spectroscopic data their relationship was established.<sup>73</sup> The full structure was elucidated later on by X-ray analysis.<sup>73a</sup>

In cytosine (151)<sup>72</sup> and related compounds the degradation starts mainly by rupture of the bond between C-7 and C-13 and proceeds by expulsion of  $\text{CH}_3\dot{\text{N}}\text{H}$  or  $\text{CH}_3\text{NHCH}_2\cdot$ , [152]→[153], [154]→[155]:



The fragmentation behavior of sparteine (156) and analogous alkaloids was elucidated with the aid of deuterated compounds.<sup>72</sup> The main fragments of mass 98 [157] and 137 [158] are formed in different ways. One of the degradation routes leading to a fragment of mass 98 is indicated in (156)→[157]→[159].

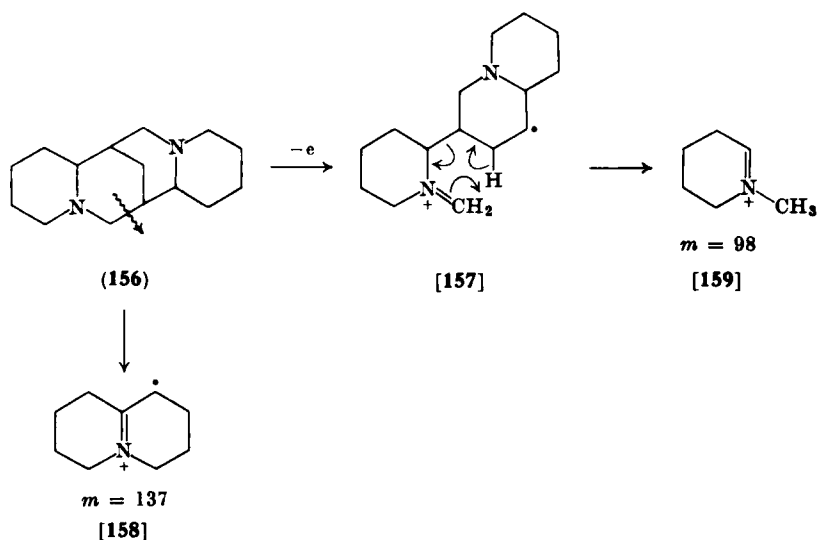
The spectra of alkaloids of the lycopodine type (160) having a hydrogen atom available in position 4 are characterized by a very easy loss of the bridge connecting C-5 and C-12. In this reaction the hydrogen at C-4 is involved: (160)→[161]→[162].<sup>74</sup> Further degradation proceeds with elimination of CO or ethylene or both.<sup>74, 75</sup>

Mass spectrometry aided in the structure determination of the

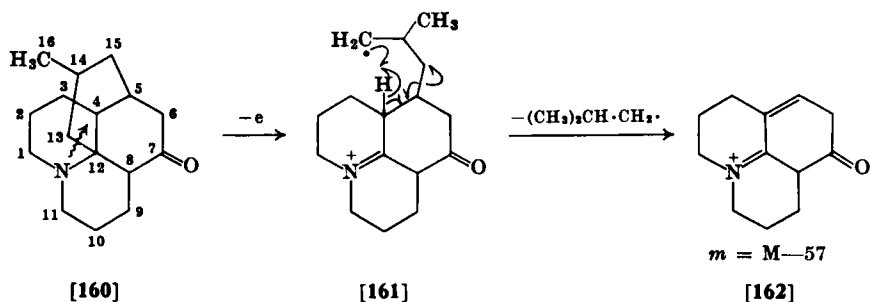
<sup>73a</sup> G. J. Birnbaum, *Tetrahedron Letters* p. 4149 (1965).

<sup>74</sup> D. B. MacLean, *Can. J. Chem.* **41**, 2654 (1963).

<sup>75</sup> A. L. Burlingame, *Conf. Mass Spectrometry, Paris*, 1964; to be published in "Advances in Mass Spectrometry," Vol. 3, Pergamon Press, Oxford.



lycopodium alkaloid lyconnitine,<sup>76</sup> ceruine,<sup>77</sup> lycoceruine<sup>77</sup>, lycofawcine<sup>77a</sup> and an unknown alkaloid, isolated from lycopodium flabelliforme.<sup>77b</sup>



e. *Amaryllidacean Alkaloids*. The interpretation of the fragmentation patterns of amaryllidacean alkaloids is rather difficult: their

<sup>76</sup> F. A. L. Anet, M. Z. Haq, N. H. Khan, W. A. Ayer, R. Hayatsu, S. Valverde-Lopez, P. Deslongchamps, W. Riess, M. Terbah, Z. Valenta, and K. Wiesner, *Tetrahedron Letters* p. 751 (1964).

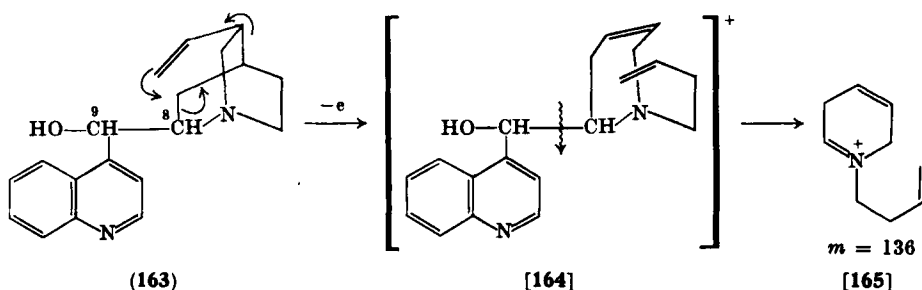
<sup>77</sup> W. A. Ayer, J. K. Jenkins, S. Valverde-Lopez, and R. H. Burnell, *Tetrahedron Letters* p. 2201 (1964).

<sup>77a</sup> W. A. Ayer, W. R. Bowman, P. Kebarle, and R. H. Brunell, *Can. J. Chem.* **43**, 328 (1965).

<sup>77b</sup> S. N. Alam, K. A. H. Adams, and D. B. MacLean, *Can. J. Chem.* **42**, 2456 (1964).

skeletons are very often cleaved by complicated rearrangement reactions which are highly sensitive even to minor changes in stereochemistry.<sup>78, 78a</sup>

f. *Quinoline Alkaloids*. Cinchonine (**163**) and other cinchona alkaloids which contain a vinyl double bond in the quinuclidine ring system exhibit in their mass spectra the most important fragment at mass 136, probably produced in the course of a rearrangement reaction, (**163**)→[**164**]→[**165**]<sup>79</sup>:



In this degradation process the stereochemistry at C-8 plays an important role, demonstrated by the fact that the fragment of mass 136 [**165**] exhibits in the mass spectrum of cinchonidine an intensity ten times that in the spectrum of cinchonine, which has the reverse stereochemistry at C-8.<sup>79</sup>

The spectrum of the tetrahydroquinoline alkaloid calycanthine has been discussed in connection with the investigation of some indoline alkaloids.<sup>80</sup>

Main fragments in the mass spectra of rutaceen alkaloids containing the 2-quinolone system were briefly reported.<sup>81</sup>

g. *Isoquinoline Alkaloids*. Key fragments of alkaloids like *N*-nornuciferine (**166**) are formed by a retro-Diels-Alder fragmentation,<sup>82</sup> (**166**)→[**167**]. The high stability of the resulting ion [**167**] permits

<sup>78</sup> A. L. Burlingame, H. M. Fales, and R. Highet, *J. Am. Chem. Soc.* **86**, 4976 (1964).

<sup>78a</sup> A. M. Duffield, R. T. Aplin, H. Budzikiewicz, C. Djerassi, C. F. Murphy, and W. C. Wildman, *J. Am. Chem. Soc.* **87**, 4902 (1965).

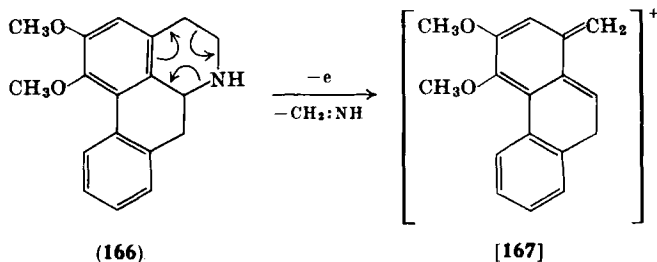
<sup>79</sup> G. Spiteller and M. Spiteller-Friedmann, *Tetrahedron Letters* p. 153 (1963).

<sup>80</sup> E. Clayton, R. I. Reed, and J. M. Wilson, *Tetrahedron* **18**, 1495 (1962).

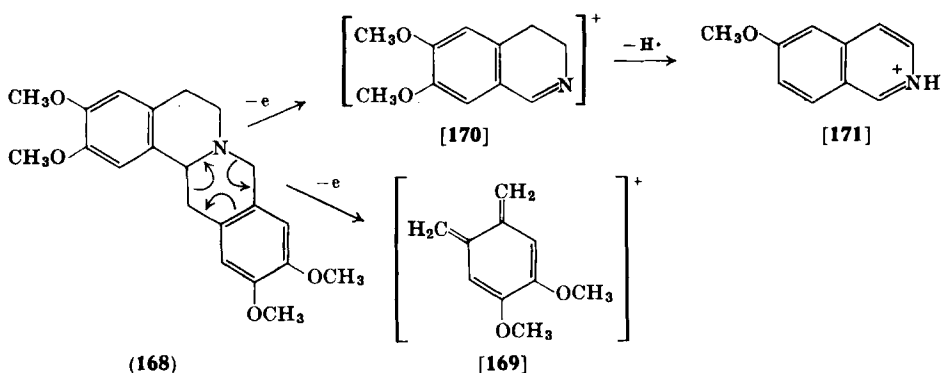
<sup>81</sup> A. Rüeggler and D. Stauffacher, *Helv. Chim. Acta* **46**, 2329 (1963).

<sup>82</sup> M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.* **85**, 2807 (1963).

the expulsion only of small substituents, e.g., methoxyl or methyl groups.

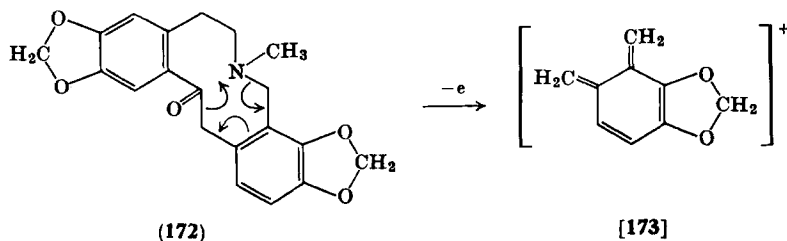


Similar degradation reactions are reported from alkaloids of the berberine group,<sup>82</sup> e.g., xylopinine,  $(168) \rightarrow [169]$ . The charge remains primarily at the nitrogen-free part of the molecule. The by-product



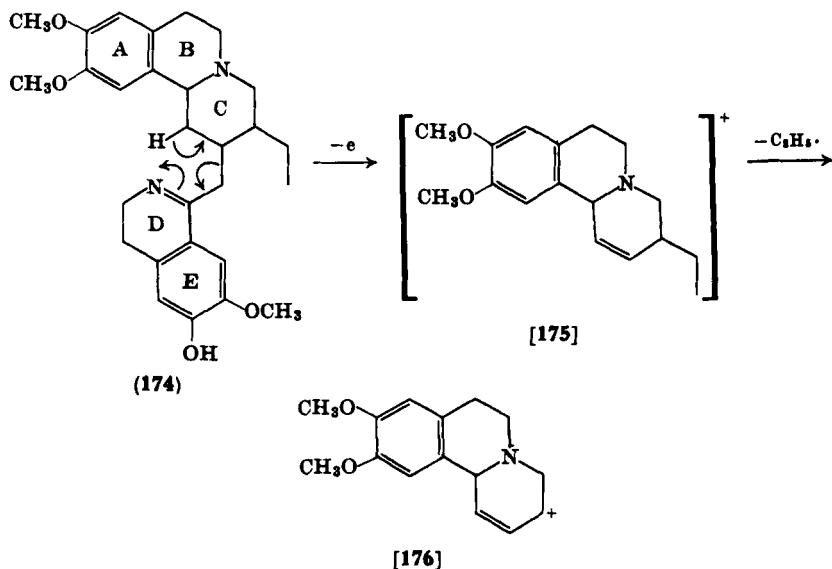
[170] is stabilized by loss of a hydrogen atom and rearrangement to an isoquinolinium ion,  $[170] \rightarrow [171]$ .

Alkaloids of the protopine class (172) are usually characterized by



a fragment of type [173], although the presence of a phenolic group may alter the main cleavage process very much.<sup>83</sup>

Compounds of the emetine class containing a double bond in ring D, e.g., psychotrine (174), are cleaved by a McLafferty rearrangement. The primary degradation product [175] can easily lose the side chain, producing an allylic carbonium ion [176].<sup>84</sup>



If ring D is saturated, as in emetine (177), this process is not possible. Here cleavage occurs at both sides of the methylene bridge connecting the two isoquinoline systems,<sup>79, 84</sup> (177)→[178], (177)→[179].

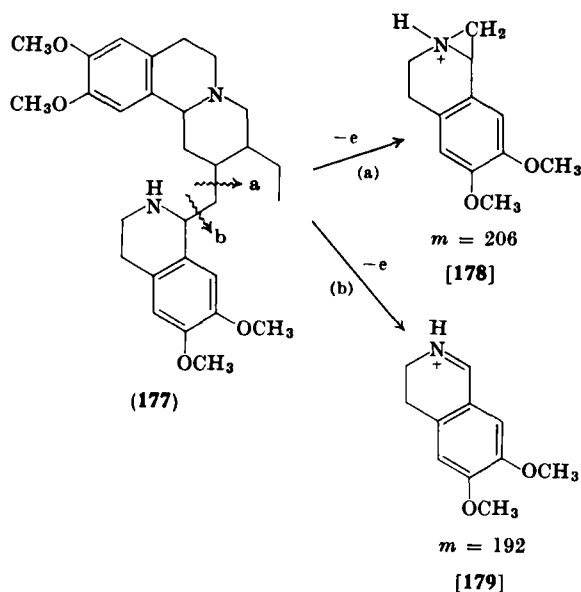
The knowledge of the emetine fragmentation pattern proved very helpful in the structure elucidation of the unknown alkaloid tubulosine.<sup>85</sup> Mass spectrometry aided very much in solving the structural problem of rhoeadine, first thought to be a tetrahydroisoquinoline alkaloid but now shown to be a representative of a new alkaloid

<sup>83</sup> L. Dolejš, V. Hanuš, and J. Slavík, *Collection Czech. Chem. Commun.* **29**, 2479 (1964).

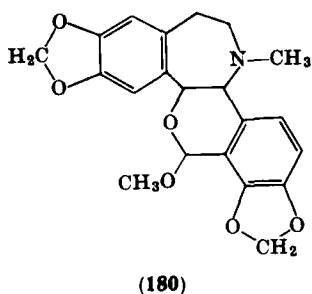
<sup>84</sup> H. Budzikiewicz, S. C. Prakrashi, and H. Vorbrüggen, *Tetrahedron* **20**, 399 (1964).

<sup>85</sup> P. Brauchli, V. Deulofeu, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.* **86**, 1964 (1964).





skeleton type which has the nitrogen situated in a seven-membered ring (180).<sup>86</sup>



h. *Tylophorine Alkaloids*. Tylophorine (181) and related alkaloids exhibit highly characteristic mass spectra (Fig. 6).<sup>87</sup> The only important degradation is a retro-Diels-Alder reaction, (181)→[182].

<sup>86</sup> F. Šantavý, J. L. Kaul, L. Hruban, L. Dolejš, V. Hanuš, K. Bláha, and A. D. Cross, *Collection Czech. Chem. Commun.* **30**, 335 (1965).

<sup>87</sup> M. Pailer and H. W. Streicher, *Monatsh.* **96**, 1094 (1965).

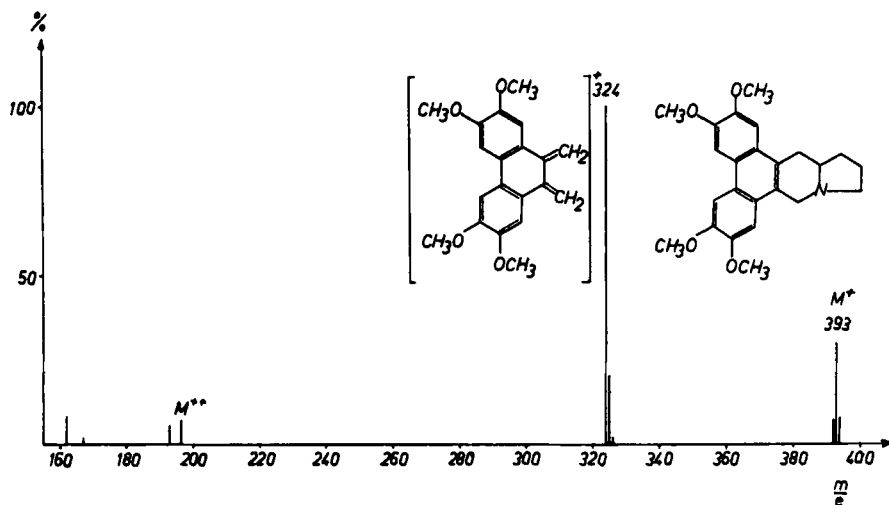
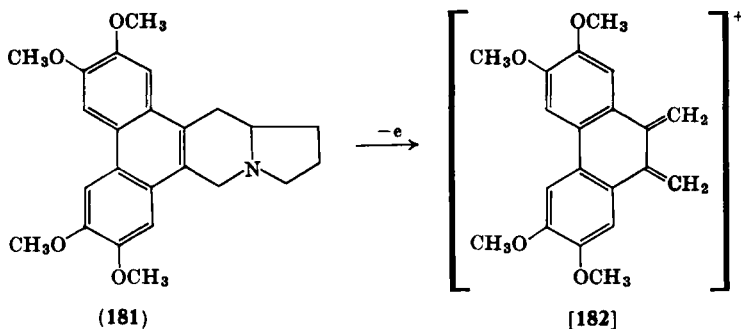


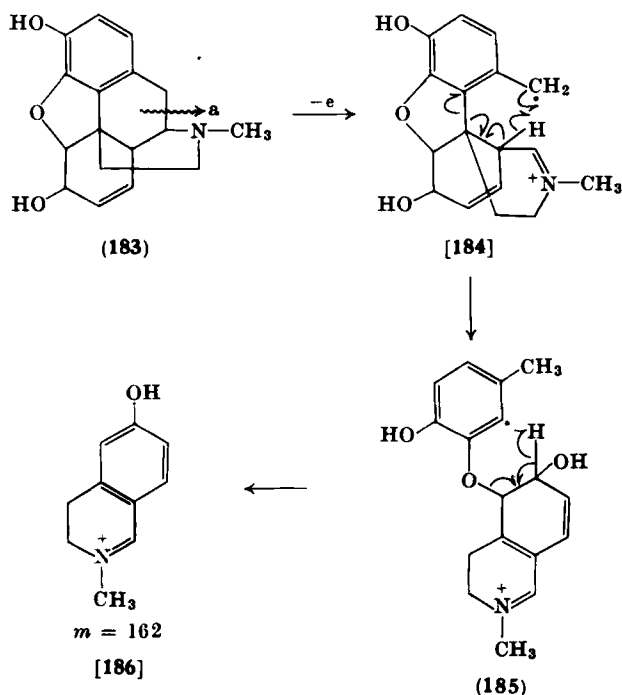
Fig. 6. Mass spectrum of tylophorine [M. Pailer and H. W. Streicher, *Monatsh.* **96**, 1094 (1965)].



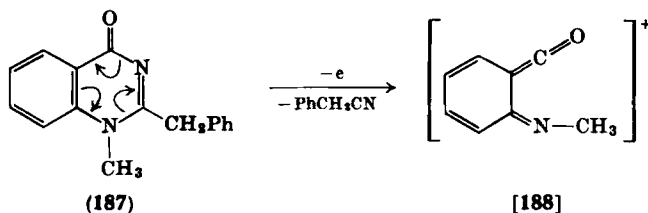
i. *Morphine Alkaloids*. Cleavage reactions of the pentacyclic morphine system are often combined with rather complex rearrangements<sup>88,88a</sup> which may be demonstrated in the case of morphine (183). By fission of bond "a" an intermediate [184] is produced which by hydrogen shift finally forms a stable ion of mass 162 [186].

<sup>88</sup> H. Audier, M. Fétizon, D. Ginsburg, A. Mandelbaum, and T. Rüll, *Tetrahedron Letters* p. 13 (1965).

<sup>88a</sup> H. Nakata, Y. Hirata, A. Tatematsu, H. Tada, and Y. K. Sawa, *Tetrahedron Letters* **829** (1965).



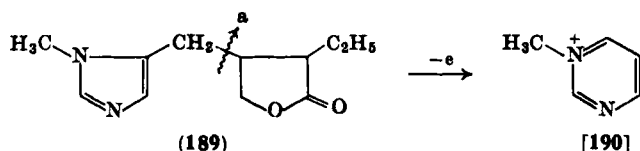
j. *Quinazolinone Alkaloids*. A retro-Diels-Alder decomposition is again the main cleavage process of alkaloids containing a quinazolinone system, like arborine, (187)  $\rightarrow$  [188]. The benzyl group is indicated by a peak at mass 91, corresponding to the tropylium ion.<sup>89</sup>



k. *Imidazole Alkaloids*. In pilocarpine (189) and analogous alkaloids the rupture of bond "a" is very favored.<sup>90</sup> The resulting fragment is believed to have the pyrimidine structure [190], in accordance with the typical behavior of five-membered alkyl-substituted heterocycles.

<sup>89</sup> S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron* **19**, 1011 (1963).

<sup>90</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **94**, 742 (1963).



1. *Indole Alkaloids*. Indole alkaloids containing an unsubstituted tetrahydro- $\beta$ -carboline system of type (191) usually exhibit in their mass spectra key fragments of mass 156, 169, 170, 184, and M-1.<sup>91, 92</sup> The M-1 fragment is produced mainly by abstraction of the hydrogen in position 3, as was shown by deuterium labeling.<sup>93</sup> The positive charge at C-3 is stabilized by resonance with the indole system and N<sub>b</sub>. For the same reason the bond between C-3 and C-14 is broken very easily, (191)→[192]. The intermediate [192] decomposes further by cleavage of the bond between C-20 and C-21. The fragment of mass 170 is probably produced by a retro-Diels-Alder fission, (191)→[194]. [194] can lose a hydrogen atom to give an ion of mass 169, [194]→[195]. The fragment of mass 156 is formed in the course of another retro-Diels-Alder reaction, (191)→[196]→[197].

If ring D is substituted, as in dihydrocorynantheol (198)<sup>94, 95</sup> or tetrahydrogeissoschizinin (199),<sup>95, 96</sup> the loss of the side chains R<sub>1</sub> or R<sub>2</sub> causes the production of additional fragments. The elimination of the side chain with the higher mass is always favored over that with the lower (Fig. 7).

The typical fragmentations pattern of the alkaloid type (199) was very useful for the structural elucidation of some minor alkaloids occurring in the bark of *Aspidosperma oblongum* A. DC. They were shown to be methoxyl and dehydro derivatives of the parent molecule.<sup>95, 96</sup>

The mass spectra of members of the yohimbine family<sup>91, 92</sup> (200) exhibit only the typical tetrahydro- $\beta$ -carboline fragments, but none which could be related to a fission reaction in ring E. So the steric differences in ring E are of minor importance for the fragmentation

<sup>91</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **93**, 795 (1962).

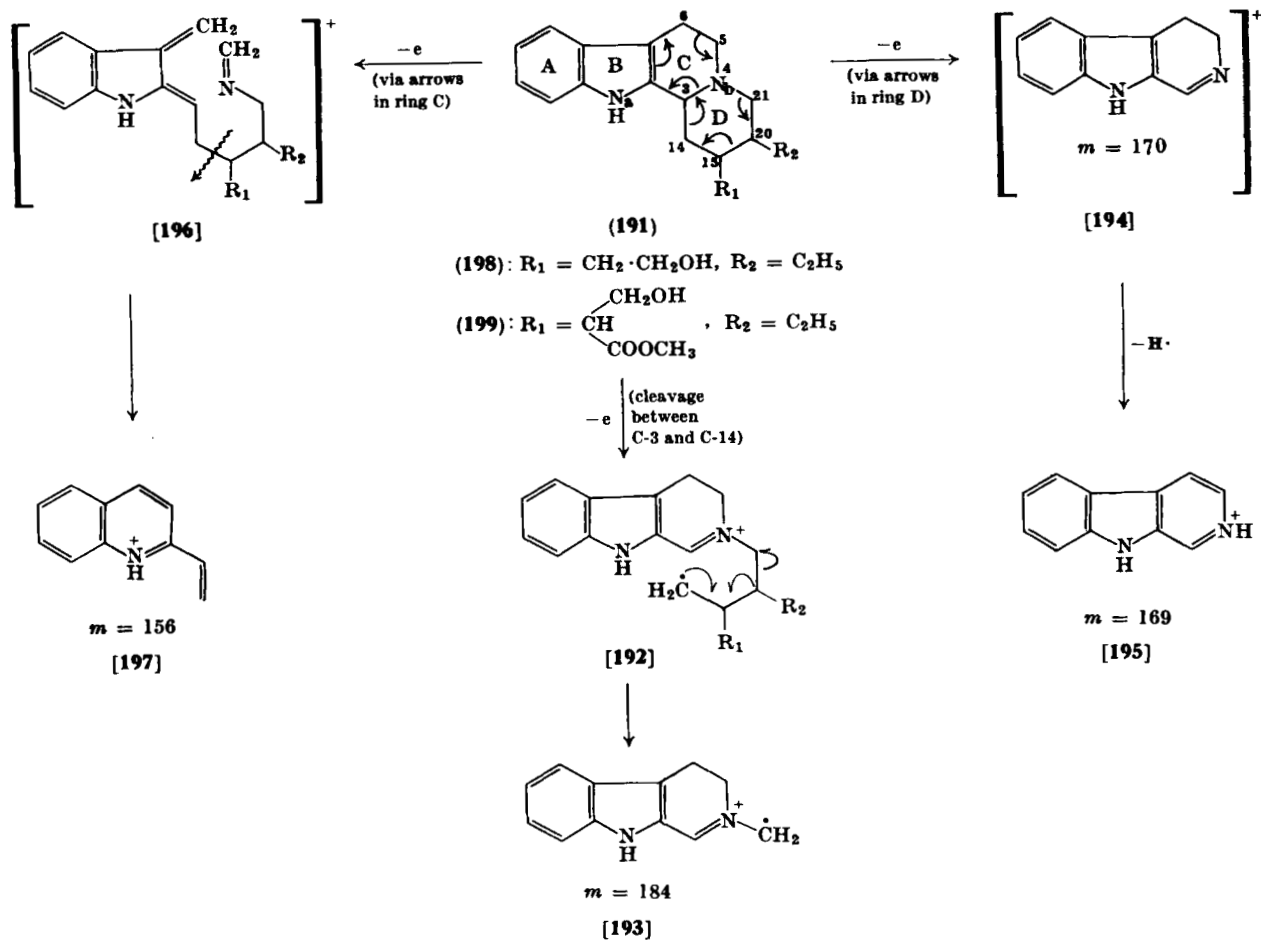
<sup>92</sup> L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrüggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *J. Am. Chem. Soc.* **84**, 2161 (1962).

<sup>93</sup> B. Gilbert, J. A. Brissolèse, N. Finch, W. I. Taylor, H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Am. Chem. Soc.* **85**, 1523 (1963).

<sup>94</sup> B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.* **27**, 4702 (1962).

<sup>95</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **94**, 779 (1963).

<sup>96</sup> G. Spiteller and M. Spiteller-Friedmann, *Ind. Chim. Belge* **29**, 337 (1964).



behavior. The presence of a  $\text{COOCH}_3$  group is easily detected by a fragment at mass  $M-59$ .

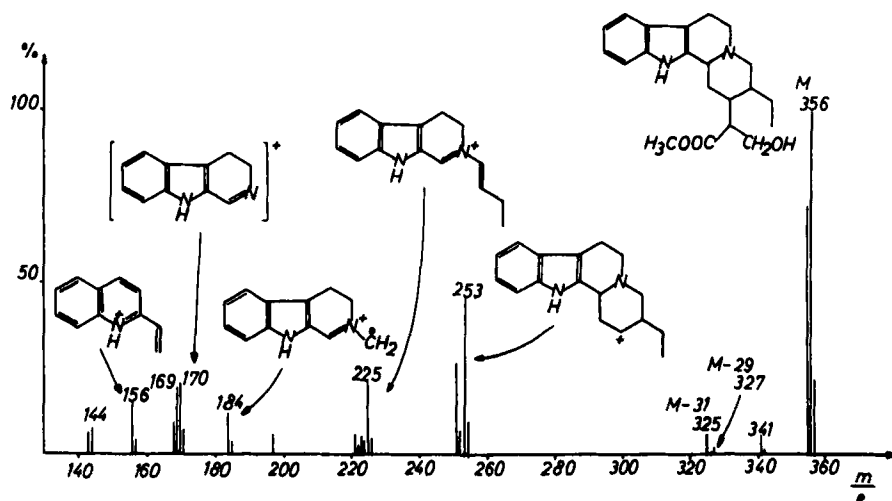
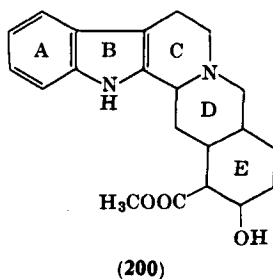


FIG. 7. Mass spectrum of tetrahydrogeissoschizin [G. Spitteller and M. Spitteller-Friedmann, *Ind. Chim. Belge* **29**, 337 (1964)].

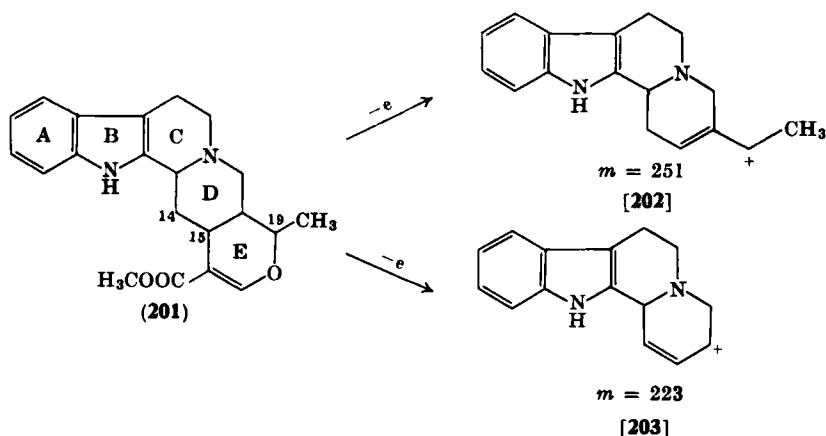
With the aid of the comparison technique, the structure of a methoxyl derivative of  $\beta$ -yohimbine was established.<sup>91</sup>



A hetero atom in ring E, e.g., in the case of tetrahydroalstonine (201), changes the fragmentation pattern drastically.<sup>49, 92, 96</sup> Two important fragments of mass 251 and 223 are produced by cleavage of ring E, (201)  $\rightarrow$  [202], (201)  $\rightarrow$  [203].

The double bond in ring E enhances the tendency for the rupture of

the bond between C-14 and C-15<sup>92</sup>; therefore the intensity of the fragment of mass 156 is very much increased, compared with yohimbine-type alkaloids. In addition, the loss of the methyl group at C-19 gives rise to a prominent peak at M-15.



Alkaloids of the ajmalicine type, which differ from the tetrahydroalstonine type only a *trans* D/E ring junction, show quite different spectra. Instead of the fragments of mass 251 [202] and 223 [203], they exhibit an intense peak at mass 225, thus differentiating these stereoisomeric types.<sup>49</sup>

The stereochemistry of C-3 in alkaloids of the tetrahydroalstonine group could also be derived from intensity differences in the mass spectra.<sup>25, 49</sup>

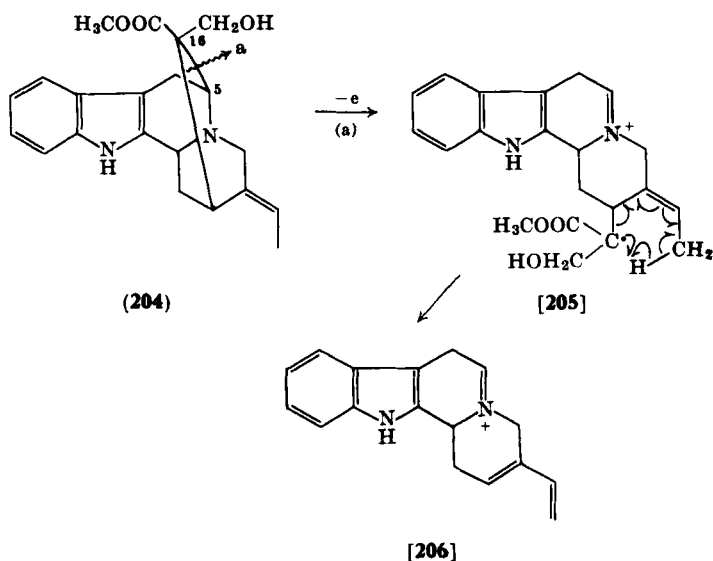
The characteristic tetrahydro- $\beta$ -carboline fragments of mass 156, 169, 170, and 184 are partly shifted if a further ring is fused on at the 5 position, e.g., in akuammidine (204). Alkaloids of this skeleton show the tetrahydro- $\beta$ -carboline fragments at mass 156, 168, 169, and 182.<sup>92, 97</sup> Usually the bridge is lost very easily.<sup>92, 97-99</sup> The most attractive mechanism for this reaction, in which a hydrogen shift is involved, seems to lead, through the cleavage of the bond between C-5 and C-16, to an intermediate [205], which may decompose further

<sup>97</sup> K. Biemann, *J. Am. Chem. Soc.* **83**, 4801 (1961).

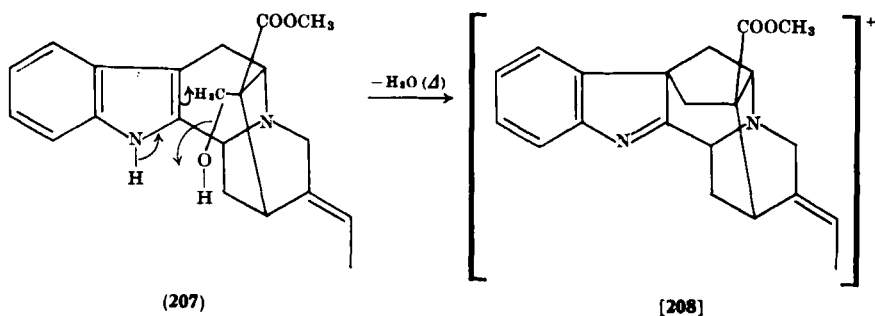
<sup>98</sup> E. Clayton, R. I. Reed, and J. M. Wilson, *Tetrahedron* **18**, 1449 (1962).

<sup>99</sup> M. Ohashi, H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Lévy, J. Gosset, J. LeMen, and M. M. Janot, *Tetrahedron* **19**, 2241 (1963).

by abstraction of a hydrogen atom from the side chain<sup>92</sup>: (204)→[205]→[206]. Other mechanisms were also proposed.<sup>92, 98</sup>



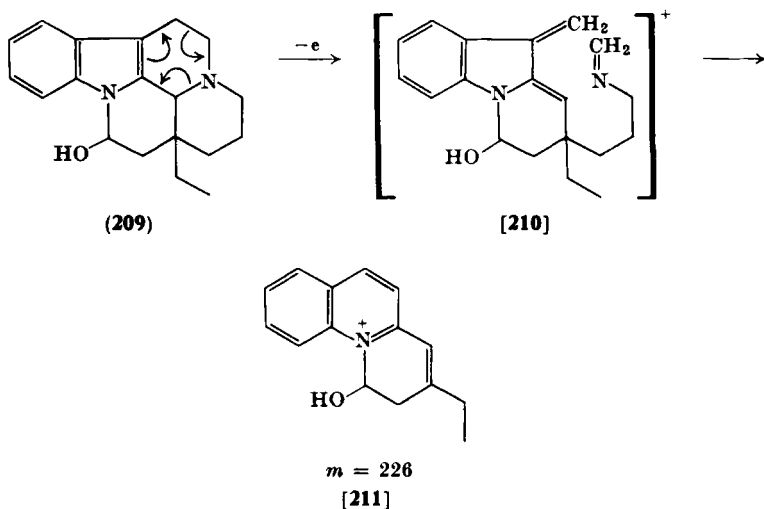
The observed differences in the mass spectra of polyneuridine and akuammidine (204), which differ only in the stereochemistry at C-16,<sup>92</sup> were later explained by a partial thermal decomposition of polyneuridine in the inlet system in which water is eliminated, (207)→[208].<sup>99</sup> The alternative position of the CH<sub>2</sub>OH group prevents this reaction in akuammidine.



The typical fragments [193], [194], [195], and [197] for a tetrahydro-β-carboline system are absent if the indole nitrogen is part of an



additional ring, as in eburnamine (209). A retro-Diels-Alder fission provides an intermediate [210] which is readily decomposed to a key fragment of mass 226 [211]. The loss of the OH group as water is favored not only by electron impact but also thermally<sup>100</sup>; using a glass inlet system, no molecular ions could be observed.<sup>100, 101</sup> Another dominant cleavage process is the elimination of the ethyl side chain.



The knowledge of the key fragmentation routes of eburnamine and some related alkaloids confirmed or elucidated the structures of the alkaloids 11-methoxy-vincamine,<sup>100</sup> vincaminine,<sup>102</sup> and vincinine,<sup>102</sup> of the same skeletal type as eburnamine. Alkaloids of the mavacurine-pleiocarpamine group (212)<sup>103</sup> are characterized by a key fragment corresponding to the loss of the ester group and

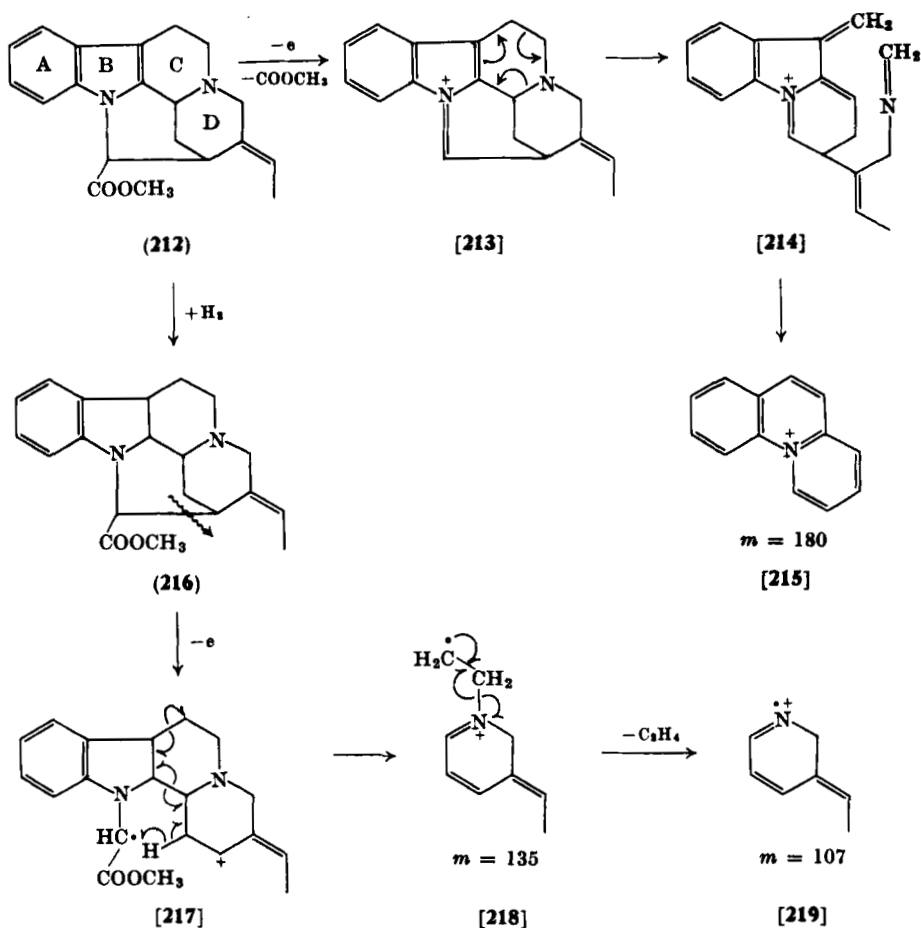
<sup>100</sup> M. Plat, D. Dohkac Manh, J. LeMen, M. M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. France* p. 1082 (1962).

<sup>101</sup> H. K. Schnoes, A. L. Burlingame, and K. Biemann, *Tetrahedron Letters* p. 993 (1962).

<sup>102</sup> J. Holubek, O. Štrouf, J. Trojáněk, A. K. Bose, and E. R. Malinowski, *Tetrahedron Letters* p. 897 (1963).

<sup>103</sup> M. Hesse, W. von Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W. I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta* **47**, 878 (1964).

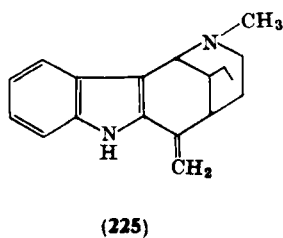
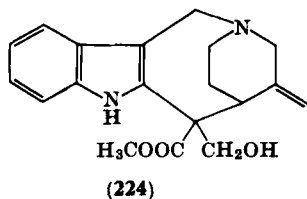
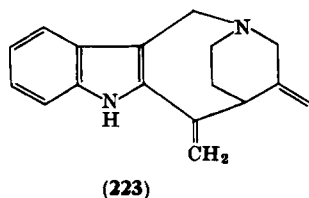
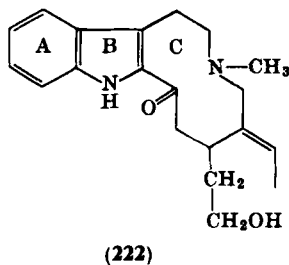
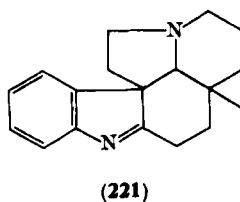
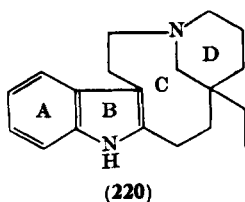
another of mass 180 containing the rings A, B, and E, which is probably produced via a retro-Diels-Alder reaction, (212)→[213]→[214]→[215].



The structure of the piperidine moiety and the presence of an unsubstituted tryptamine bridge in alkaloids of the mavacurine-pleiocarpamine class can be proved by a catalytic reduction to the corresponding indolines, which show very different spectra because now the main fragments contain ring D,<sup>103</sup> (212)→(216)→[217]→[218]→[219]. The reduction of indole to indoline alkaloids seems an attractive route for the structure determination of those alkaloids.<sup>25</sup>

The indole alkaloids so far discussed all have a tetrahydro- $\beta$ -carboline system. The main fragments of these alkaloids contain the indole part of the molecules. This situation is changed in alkaloids which have a larger ring C or an indoline system, permitting the production of fragments characteristic of both the indole and piperidine moieties.

The spectrum of quebrachamine (220) thus shows predominant fission of bonds in ring C. Dependent on the localization of the charge,



either indole-ring- or piperidine-ring-containing fragments are formed.

The structure of quebrachamine was proved by comparing its mass spectrum with that of methoxyquebrachamine synthesized from deacetylaspidospermine via its dehydro product.<sup>104</sup>

<sup>104</sup> K. Biemann and G. Spiteller, *Tetrahedron Letters* p. 299 (1961); *J. Am. Chem. Soc.* **84**, 4578 (1962).

Mass spectrometry was very helpful in determination of the structures of vincaminorine,<sup>105</sup> vincaminoreine,<sup>105</sup> *ind-N*-methylquebrachamine,<sup>105, 106</sup> and a degradation product of rhazidigenine,<sup>107</sup> alkaloids closely related to quebrachamine (220) and the dehydro product (221).

Mass spectrometry was also used to confirm the structure of burnamicine (222), which gives also fragments mainly by rupture of bonds in ring C,<sup>108</sup> and another 2-acylindole alkaloid, picraphylline.<sup>109</sup>

Mass spectrometry aided also in the structure determination of apparicine (223),<sup>110</sup> vallesamine (224),<sup>111</sup> and *o*-acetylvallesamine.<sup>111</sup> The spectrum of uleine (225)<sup>112</sup> aided in the identification of naturally occurring derivatives thereof.<sup>113</sup>

A characteristic fragmentation pattern is reported for vobasine (226),<sup>114, 115</sup> a 2-acylindole alkaloid. The fission of the bond between C-5 and C-6 produces intermediate [227], which is decomposed by a McLafferty rearrangement,<sup>115</sup> [227]→[228].

The presence of the carbomethoxy group can be deduced from a fragment of mass M-59. Either from this fragment<sup>115</sup> or from [228]<sup>114</sup> the cleavage product of mass 122 [229] may be derived. The indole fragments are produced with but low probability.

The absence of the carbonyl group in vobasinol (230) causes another type of rearrangement of the primary degradation product [231],<sup>115</sup> (230)→[231]→[232].

A second prominent fragment of mass 180 is probably formed by a

<sup>105</sup> J. Trojáněk, O. Štrouf, K. Bláha, L. Dolejš, and V. Hanuš, *Collection Czech. Chem. Commun.* **29**, 1904 (1964).

<sup>106</sup> J. Mokřý and I. Kompiš, *Chem. Zvesti* **17**, 852 (1963).

<sup>107</sup> M. Spiteller-Friedmann, R. Kaschnitz, G. Spiteller, A. Chatterjee, N. Aditchaudhury, and G. Ganguli, *Monatsh.* **95**, 1228 (1964).

<sup>108</sup> M. F. Bartlett and W. I. Taylor, *J. Am. Chem. Soc.* **85**, 1203 (1963).

<sup>109</sup> J. Lévy, G. Ledouble, J. LeMen, and M. M. Janot, *Bull. Soc. Chim. France* p. 1917 (1964).

<sup>110</sup> J. A. Joule, H. Monteiro, L. J. Durham, B. Gilbert, and C. Djerassi, *J. Chem. Soc.* p. 4773 (1965).

<sup>111</sup> A. Walser and C. Djerassi, *Helv. Chim. Acta* **47**, 2072 (1964).

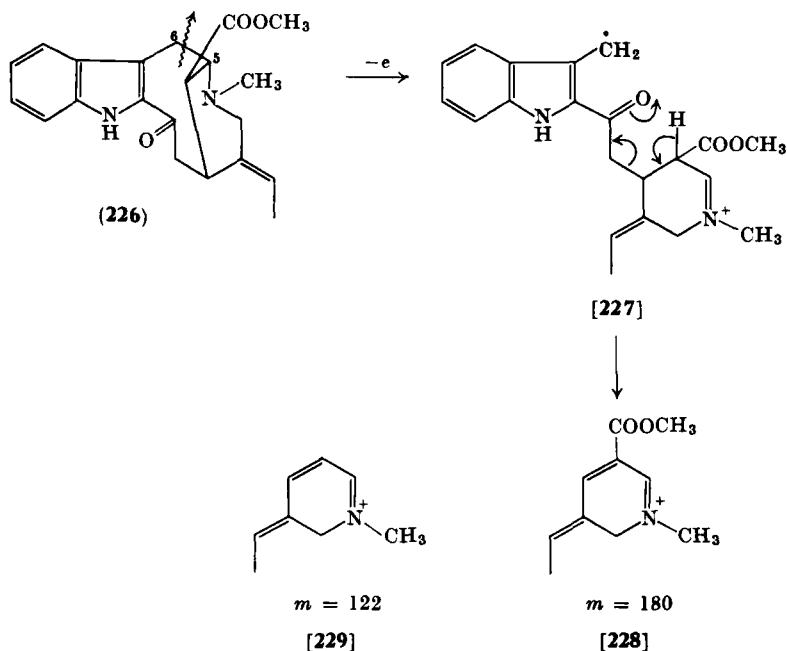
<sup>112</sup> J. A. Joule and C. Djerassi, *J. Chem. Soc.* p. 2777 (1964).

<sup>113</sup> M. Ohashi, J. A. Joule, B. Gilbert, and C. Djerassi, *Experientia (Basel)* **20**, 263 (1964).

<sup>114</sup> H. Budzikiewicz, C. Djerassi, F. Puisieux, F. Percheron, and J. Poisson, *Bull. Soc. Chim. France* p. 1899 (1963).

<sup>115</sup> U. Renner, D. A. Prins, A. L. Burlingame, and K. Biemann, *Helv. Chim. Acta* **46**, 2186 (1963).

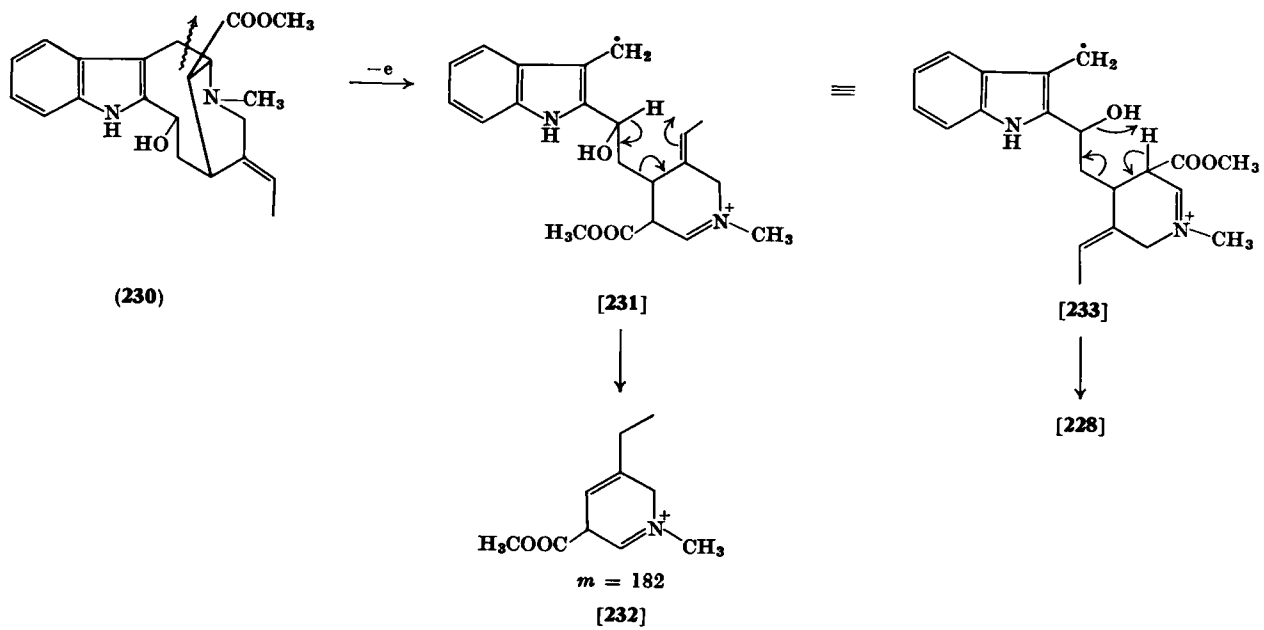
similar rearrangement process as was described above in the case of vobasine, [233]→[228].



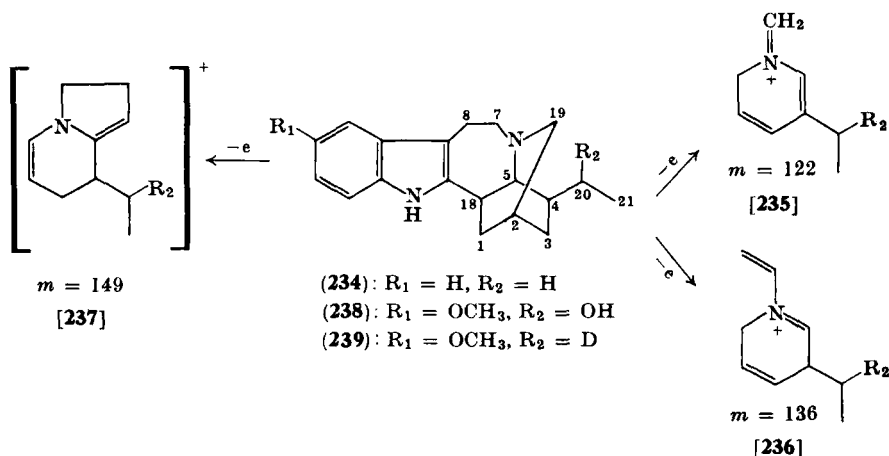
Alkaloids of the ibogamine type (234) show in their mass spectra fragments corresponding to the indole and piperidine parts of the molecule, and therefore mass spectrometry is particularly useful for their structural elucidation.<sup>114, 116</sup> A fragment containing the indole moiety is found at mass 156 and assumed to be a vinylquinolinium ion [197]. The most important fragments must be ascribed to the piperidine part of the molecule. The mechanisms which lead to their production are not absolutely certain, although the structures of the fragments of mass 122 [235], 136 [236], and 149 [237] are rendered probable as a result of labeling experiments with deuterium.<sup>116</sup>

The loss of a methyl group (C-21) is much preferred to that of an ethyl group although a primary carbonium ion is produced. This was explained by the lone electron pair of the nitrogen stabilizing the positive charge at C-20,<sup>116</sup> forming a four-membered ring.

<sup>116</sup> K. Biemann and M. Spiteller-Friedmann, *Tetrahedron Letters* p. 68 (1961); *J. Am. Chem. Soc.* **83**, 4805 (1961).



The uncertain position of the hydroxy group in the side chain of iboxygaine (**238**) was determined by a mass spectrometric investigation of the  $\text{LiAlD}_4$ -reduction product (**239**) of its tosylate. A peak



at M-15 in the spectrum of the deuterated ibogamine (**239**) proved that the deuterium, and hence the OH, could not be situated at C-21<sup>116</sup> because the loss of the  $\text{CH}_3$  group from the methoxyl function is not possible. Further, the peak at M-29 ( $\text{M} - \text{C}_2\text{H}_5$ ) in the spectrum of the unlabelled reduction product was found in the deuterated sample at M-30, indicating the loss of  $\text{C}_2\text{H}_4\text{D}$ .

The "double alkaloids" voacamine and voacorine exhibit in their spectra a fragmentation pattern very similar to those of the two parent alkaloids from which they are formed. It was possible to deduce the structure of voacorine by comparing its mass spectrum with that of voacamine, of which the structure was already known.<sup>114</sup>

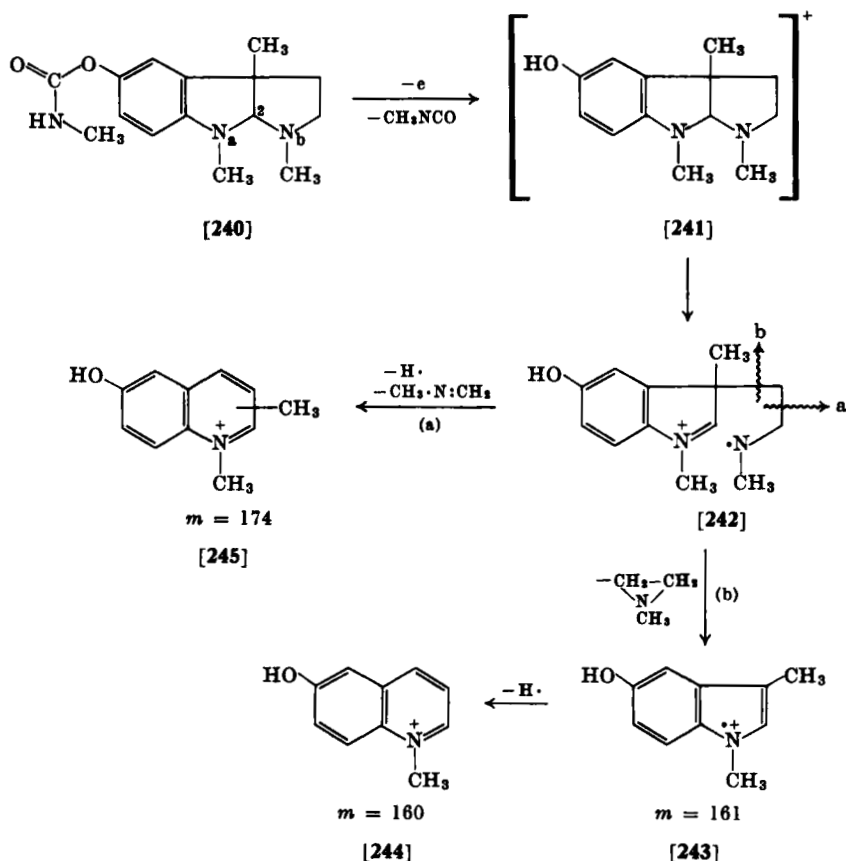
In an investigation of another alkaloid of the dimeric type, vinblastine, high-resolution mass spectrometry was extensively used to determine the molecular formulas of the molecule ion and its cleavage products.<sup>117</sup> This was very helpful in the structure determination.<sup>118</sup> The structure elucidation of villastonine, also an indole alkaloid of the

<sup>117</sup> P. Bommer, W. J. McMurry, and K. Biemann, *J. Am. Chem. Soc.* **86**, 1439 (1964).

<sup>118</sup> N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.* **86**, 1441 (1964).

dimeric type, was carried out mainly by mass spectrometry.<sup>118a</sup> The spectrum of a degradation product of villastonine called macroline facilitated the structure determination of the naturally occurring alkaloid alstophilline.<sup>118b</sup>

m. *Indoline Alkaloids*. Physostigmine and related alkaloids<sup>119, 120</sup> readily eliminate one molecule of methyl isocyanate, (240)→[241]. By fission of the bond between C-2 and N<sub>b</sub> in [241], an intermediate is



<sup>118a</sup> M. Hesse, H. Hürzeler, C. W. Gemenden, B. S. Joshi, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta* **48**, 689 (1965).

<sup>118b</sup> T. Kishi, M. Hesse, C. W. Gemenden, W. I. Taylor, and H. Schmid, *Helv. Chim. Acta* **48**, 1349 (1965).

<sup>119</sup> G. Spiteller and M. Spiteller-Friedmann, *Tetrahedron Letters* p. 147 (1963).

<sup>120</sup> E. Clayton and R. I. Reed, *Tetrahedron* **19**, 1345 (1963).



produced which is further cleaved with loss of  $\text{CH}_3 \cdot \text{N}:\text{CH}_2$  and a hydrogen atom and rearrangement to a quinolinium ion,  $[\mathbf{241}] \rightarrow [\mathbf{242}] \rightarrow [\mathbf{245}]$ .

By expulsion of one molecule of *N*-methylethyleneimine from  $[\mathbf{242}]$  an indole fragment is formed  $[\mathbf{243}]$ , which may rearrange with loss of a hydrogen atom to a quinolinium ion of mass 160  $[\mathbf{244}]$ .

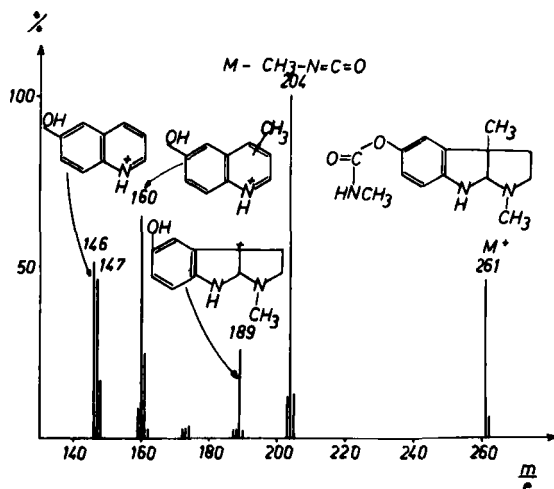


FIG. 8. Mass spectrum of noreserine [G. Spiteller and M. Spiteller-Friedmann, *Ind. Chim. Belge* **29**, 337 (1964)].

The typical physostigmine fragmentation pattern permitted the structural elucidation of noreserine<sup>96</sup> (Fig. 8) and eseramine.<sup>121</sup>

Double alkaloids of the physostigmine type, like folicanthine, are cleaved preferentially at the bond which connects the two halves of the molecule.<sup>80</sup>

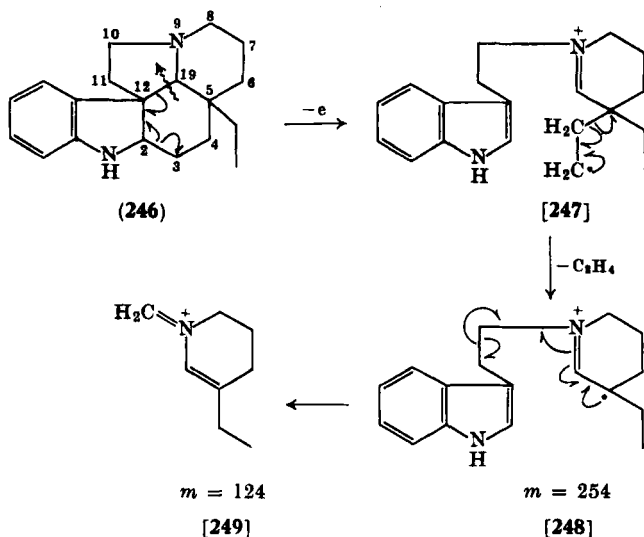
Aspidospermidine (**246**) and related alkaloids exhibit characteristic spectra, containing fragments consisting of the piperidine and the indole parts of the molecule. By rupture of the C-12—C-19 and C-2—C-3 bonds a stable indole system is formed,  $(\mathbf{246}) \rightarrow [\mathbf{247}]$ .<sup>122, 123</sup>

<sup>121</sup> B. Robinson and G. Spiteller, *Chem. Ind. (London)* p. 459 (1964).

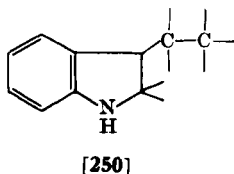
<sup>122</sup> K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *Tetrahedron Letters* p. 485 (1961); *J. Am. Chem. Soc.* **85**, 631 (1963).

<sup>123</sup> C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. LeCount, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta* **46**, 742 (1963).

The loss of one molecule of ethylene, with subsequent cleavage of the C-10—C-11 bond, is preferred, [247]→[248]→[249].



The fragment [249] of mass 124 is of unusually high intensity, and this is a criterion for aspidospermidine-type alkaloids. If the positive charge is first localized on the indole moiety, fission starts with the cleavage of the C-2—C-3 bond. By further fission of the C-10—C-11 bond an indole fragment of mass 130 is produced which probably rearranges to the more stable quinolinium ion [60]. Two fragments of mass 143 and 144, very often found in indoline alkaloids containing a tryptamine bridge, are probably formed by fission of the C-10—N-9 bond. Although their structures are not yet fully clarified, their appearance is a strong indication for the structure element [250]:



By comparison, a number of minor alkaloids occurring together with aspidospermine in the bark of *Quebracho blanco* were identified as  $N_\alpha$ -acetyl and/or methoxyl derivatives of aspidospermidine.<sup>122</sup>

In the same way pyrifolidine,<sup>124</sup> spegazzinine and spegazzinidine,<sup>125, 126</sup> limaspermine,<sup>127</sup> 3'-methoxylimapodine,<sup>128</sup> vindoline<sup>129</sup> (which later proved to be a mixture of two alkaloids differing one from another by a methoxy group,<sup>130</sup> vindorosine,<sup>130</sup> and demethoxypalosine<sup>131</sup> were shown to have an aspidospermidine skeleton.

A double bond in position 2, 3 in alkaloids of the aspidospermidine type, as in vincadifformine, prevents the production of the characteristic fragment of mass 124 [249], but an easy correlation is possible after the hydrogenation of the double bond, as was shown for vincadifformine,<sup>132</sup> minovincinine,<sup>133</sup> minovincine,<sup>133</sup> tabersonine,<sup>134</sup> lochnericine,<sup>135</sup> and lochnerinine.<sup>135</sup>

The typical cleavage reactions of the aspidospermidine-type alkaloids are not changed if the carbon C-21 is connected through an oxygen bridge to C-19, thus forming an additional ring (251). The fragment [249] alone is shifted by 14 mass numbers to mass 138 [252] (R = H<sub>2</sub>). This permitted the structural elucidation of the following alkaloids of type (251): aspidoalbine,<sup>136</sup> 1-acetylaspidoalbidine,<sup>137</sup> 1-acetyl-17-hydroxyaspidoalbidine,<sup>137</sup> and aspidolimidine.<sup>131</sup>

<sup>124</sup> C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson, and K. Biemann, *Experientia* **17**, 162 (1961).

<sup>125</sup> C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi, and R. A. Corral, *J. Am. Chem. Soc.* **84**, 3480 (1962).

<sup>126</sup> C. Djerassi, H. W. Brewer, O. O. Orazi, and R. A. Corral, *Experientia* **18**, 113 (1962).

<sup>127</sup> M. Pinar, W. von Philipsborn, W. Vetter, and H. Schmid, *Helv. Chim. Acta* **45**, 2260 (1962).

<sup>128</sup> M. Pinar and H. Schmid, *Ann.* **668**, 97 (1963).

<sup>129</sup> M. Gorman, N. Neuss, and K. Biemann, *J. Am. Chem. Soc.* **84**, 1058 (1962).

<sup>130</sup> B. K. Moza, J. Trojáněk, V. Hanuš, and L. Dolejš, *Collection Czech. Chem. Commun.* **29**, 1913 (1964).

<sup>131</sup> B. Gilbert, J. A. Brissolèse, J. M. Wilson, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Chem. Ind. (London)*, p. 1949 (1962).

<sup>132</sup> C. Djerassi, H. Budzikiewicz, J. M. Wilson, J. Gosset, J. LeMen, and M. M. Janot, *Tetrahedron Letters* p. 235 (1962).

<sup>133</sup> M. Plat, J. LeMen, M. M. Janot, H. Budzikiewicz, J. M. Wilson, L. J. Durham, and C. Djerassi, *Bull. Soc. Chim. France* p. 2237 (1962).

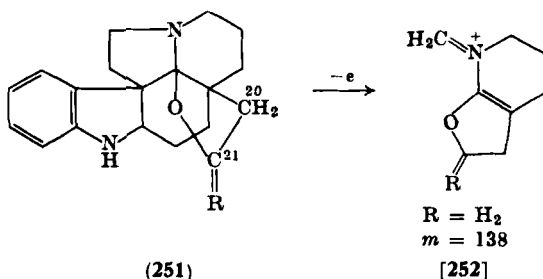
<sup>134</sup> M. Plat, J. LeMen, M. M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Letters* p. 271 (1962).

<sup>135</sup> B. K. Moza, J. Trojáněk, A. K. Bose, K. G. Das, and P. Funke, *Tetrahedron Letters* p. 2561 (1964); *Lloydia* **27**, 416 (1964).

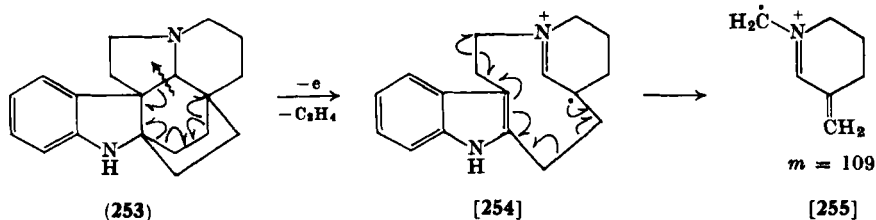
<sup>136</sup> C. Djerassi, L. D. Antonaccio, H. Budzikiewicz, J. M. Wilson, and B. Gilbert, *Tetrahedron Letters* p. 1001 (1962).

<sup>137</sup> K. S. Brown, Jr., H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters* p. 1731 (1963).

The fragmentation pattern differs much more if in (251)  $R = O$ , e.g., in dichotamine,<sup>137</sup> because now the elimination of  $CO_2$  is favored.



The connection of C-21 to C-2 as in aspidofractinine<sup>123, 138</sup> (253) prevents the formation of the fragment [249] in the same way as shown for aspidospermidine. Hence the intensity of the primary degradation product [254], formed by loss of ethylene, is enhanced. It decomposes by fission of the C-3—C-4 and C-10—C-11 bonds, producing a fragment of mass 109 [255].<sup>123</sup>



The abundance of the fragment of mass 124 [249] produced by a hydrogen shift<sup>123</sup> is much lower than in aspidospermidine. The typical aspidofractinine pattern facilitated the structure determination of pyrifoline,<sup>139</sup> refractidine,<sup>139</sup> refractine,<sup>140</sup> aspidofractine,<sup>140</sup> aspidofiline,<sup>141</sup> and kopsinine.<sup>123</sup>

A carbonyl group in position 3 of the aspidospermidine skeleton (246) prevents the loss of the C-2—C-3 bridge, because in the primary

<sup>138</sup> G. Spitteller, *Z. Anal. Chem.* **197**, 1 (1963).

<sup>139</sup> B. Gilbert, J. M. Ferreira, R. J. Owellen, C. E. Swanholm, H. Budzikiewicz, L. J. Durham, and C. Djerassi, *Tetrahedron Letters* p. 59 (1962).

<sup>140</sup> C. Djerassi, T. George, N. Finch, H. F. Lodish, H. Budzikiewicz, and B. Gilbert, *J. Am. Chem. Soc.* **84**, 1500 (1962).

<sup>141</sup> C. Djerassi, R. J. Owellen, J. M. Ferreira, and L. D. Antonaccio, *Experientia* **18**, 397 (1962).

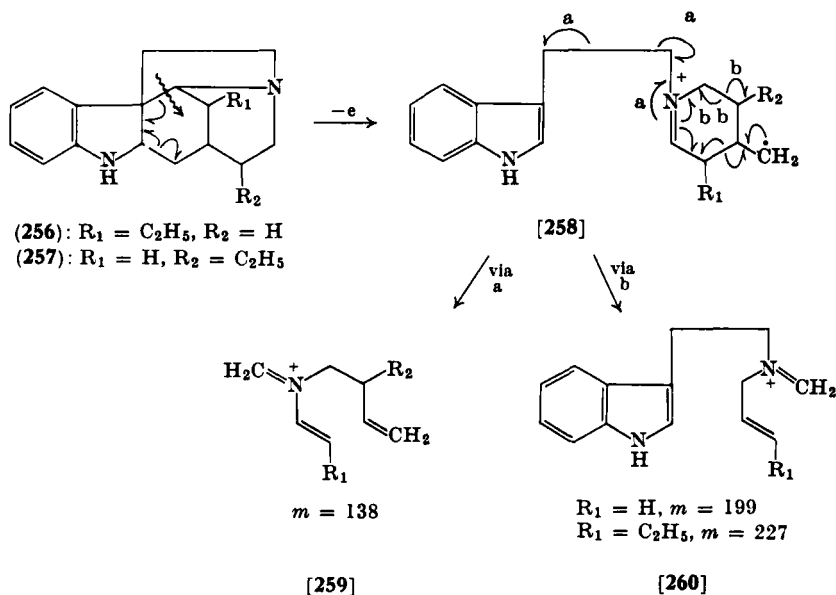
degradation product [247] the loss of a stable CO molecule is more favored than that of  $\text{CH}_2=\text{C}=\text{O}$ . Therefore a fragment of mass 138 is formed instead of one of mass 224.<sup>125</sup>

The presence of an additional ring connected to the tryptamine bridge changes the aspidospermidine fragmentation pattern drastically, as was demonstrated for kopsine<sup>142</sup> and vindolinine.<sup>143, 144</sup>

This knowledge of the fragmentation pattern of vindolinine enabled the structure determination of the related alkaloid tuboxenine.<sup>145</sup>

The typical aspidospermidine pattern could also not be observed in the spectra of alkaloids related to obscurinervine.<sup>146</sup>

Compounds with the skeleton of a dihydroaspidospermatidine (256) (Fig. 9) or a tetrahydrodecabomethoxyakummicine (257)



<sup>142</sup> G. Spiteller, A. Chatterjee, A. Bhattacharya, and A. Deb, *Monatsh.* **93**, 1220 (1962).

<sup>143</sup> C. Djerassi, S. E. Flores, H. Budzikiewicz, J. M. Wilson, L. J. Durham, J. LeMen, M. M. Janot, M. Plat, M. Gorman, and N. Neuss, *Proc. Natl. Acad. Sci. U.S.A.* **48**, 113 (1962).

<sup>144</sup> C. Djerassi, M. Cereghetti, H. Budzikiewicz, M. M. Janot, M. Plat, and J. LeMen, *Helv. Chim. Acta* **47**, 827 (1964).

<sup>145</sup> C. Kump, J. Seibl, and H. Schmid, *Helv. Chim. Acta* **47**, 358 (1964).

<sup>146</sup> K. S. Brown, Jr., and C. Djerassi, *J. Am. Chem. Soc.* **86**, 2451 (1964).

undergo cleavage reactions similar to those of aspidospermidine. Alkaloids of these types exhibit in their spectra the same indole fragments at mass 130 [60], 143, and 144. The piperidine fragments are shifted to mass 138, because now the loss of ethylene is not possible from the primary degradation product [258],<sup>122,147</sup> (256)→[258]→[259].

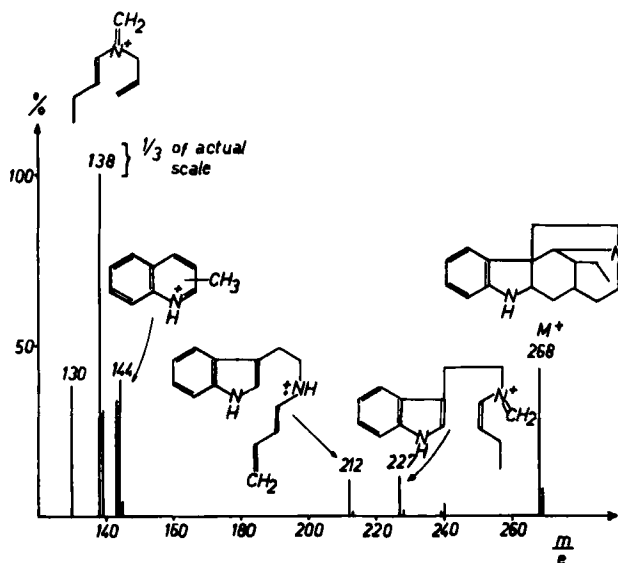


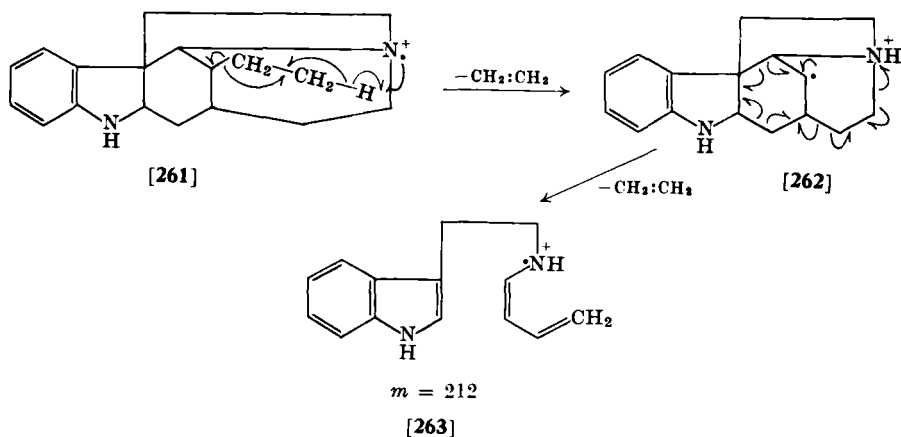
FIG. 9. Mass spectrum of dihydroaspidospermatidine [K. Biemann, M. Spiteller-Friedmann, and G. Spiteller, *Tetrahedron Letters* p. 485 (1961); *J. Am. Chem. Soc.* **85**, 631 (1963)].

The intermediate [258] can also be cleaved with formation of the fragment [260] which distinguishes the aspidospermatidine and the akuammicine families,<sup>122</sup> [258]→[260].

The compounds (256) and (257) show in their mass spectra a considerable peak at M-28, indicating that the elimination of ethylene is still an important degradation process. The loss of ethylene may be explained by assuming a hydrogen shift in the molecular ion, [261]→[262]. The intermediate [262] can now lose another ethylene

<sup>147</sup> H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Lévy, J. LeMen, and M. M. Janot, *Tetrahedron* **19**, 1265 (1963).

molecule to give a fragment of mass 212, [262]→[263]. This process is not possible in the case of compound (257).



Double bonds, especially in position 2,3, hinder the formation of the typical key fragments of these alkaloid groups. Therefore for correlation a preliminary hydrogenation is always advisable.

Compounds having an aspidospermatidine skeleton were found as minor alkaloids in the bark of *Quebracho blanco* and identified by the comparison technique.<sup>122</sup> An aspidospermatidine skeleton was also determined with the aid of the mass spectrometry for condylocarpine,<sup>148,149</sup> and limatine<sup>149a</sup> while echitamidine,<sup>150</sup> lochneridine,<sup>151</sup> mossambine,<sup>152</sup> compactinervine,<sup>153</sup> acetyldiaboline,<sup>153a</sup> henning-

<sup>148</sup> K. Biemann, A. L. Burlingame, and D. Stauffacher, *Tetrahedron Letters* p. 527 (1962).

<sup>149</sup> A. Sandoval, F. Walls, J. N. Shoolery, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters* p. 409 (1962).

<sup>149a</sup> M. Pinar, B. W. Bycroft, J. Seibl, and H. Schmid, *Helv. Chim. Acta* **48**, 822 (1965).

<sup>150</sup> C. Djerassi, Y. Nakagawa, H. Budzikiewicz, J. M. Wilson, J. LeMen, J. Poisson, and M. M. Janot, *Tetrahedron Letters* p. 653 (1962).

<sup>151</sup> Y. Nakagawa, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Chem. Ind. (London)* p. 1986 (1962).

<sup>152</sup> X. Monseur, R. Goutarel, J. LeMen, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *Bull. Soc. Chim. France* p. 1088 (1962).

<sup>153</sup> C. Djerassi, Y. Nakagawa, J. M. Wilson, H. Budzikiewicz, B. Gilbert, and L. D. Antonaccio, *Experientia* **19**, 467 (1963).

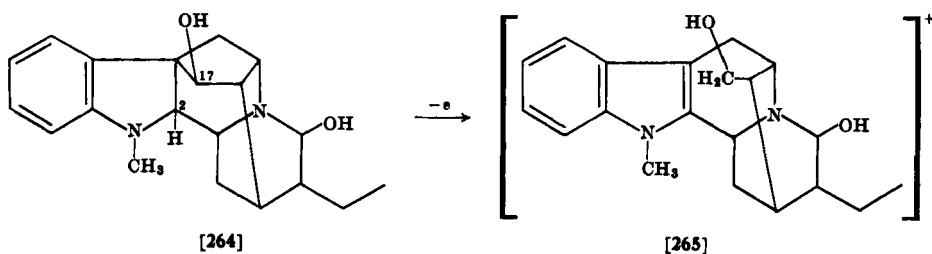
<sup>153a</sup> H. Müller, M. Hesse, P. Waser, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **48**, 320 (1965).

soline,<sup>153b</sup> and henningsamine<sup>153c</sup> were shown to have akuammicine-type skeletons.

Comprehensive surveys of the structural determination of aspidospermatidine and akuammicine alkaloids have been given by Djerassi<sup>154</sup> and Janot.<sup>155</sup>

Alkaloids related to ajmaline (264) and its 2-epi-isomer show very different mass spectra.<sup>156, 157</sup> Ajmaline-type alkaloids are characterized mainly by fragments containing the indole part of the molecule.<sup>119, 156</sup> Peaks at mass 144 and 157 represent *N*-methyl homologs of the indole fragments of mass 130 [60] and 143 discussed earlier. Besides this there are fragments of the  $\beta$ -carboline type of mass 182 and 183 (they are the *N*-methyl homologs of the fragments of mass 168 and 169). Later it was shown by high-resolution mass spectrometry that the peak at mass 182 corresponds only partly to a  $\beta$ -carboline fragment of formula  $C_{12}H_{10}N_2$ : a species  $C_{13}H_{12}N$  is also present.<sup>156</sup>

By contrast, main fragments of alkaloids of the epiajmaline type are also formed from the piperidine part of the molecule. The difference in the fragmentation behavior of the epimers was explained<sup>157</sup> by assuming that in ajmaline-type alkaloids the hydrogen in position 2 is shifted to C-17, producing an indole derivative which is now cleaved, (264)  $\rightarrow$  [265]:



<sup>153b</sup> K. Biemann, J. S. Grossert, J. Occolowitz, and F. L. Warren, *J. Chem. Soc.* p. 2818 (1965).

<sup>153c</sup> K. Biemann, J. S. Grossert, J. M. Hugo, J. Occolowitz, and F. L. Warren, *J. Chem. Soc.* p. 2814 (1965).

<sup>154</sup> C. Djerassi, *Pure Appl. Chem.* **6**, 575 (1963).

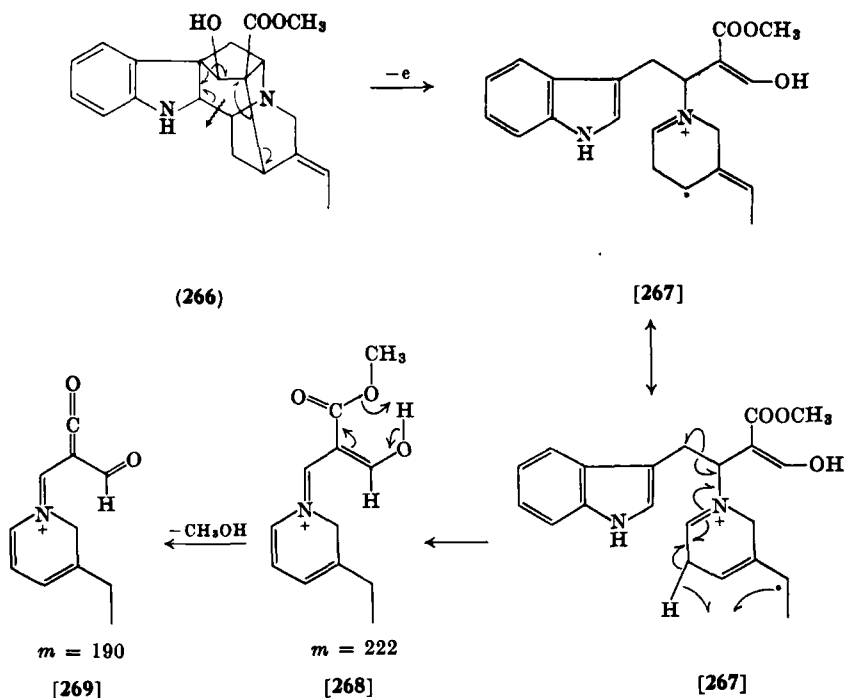
<sup>155</sup> M. M. Janot, *Pure Appl. Chem.* **6**, 635 (1963).

<sup>156</sup> K. Biemann, P. Bommer, A. L. Burlingame, and W. J. McMurphy, *Tetrahedron Letters* p. 1969 (1963).

<sup>157</sup> K. Biemann, P. Bommer, A. L. Burlingame, and W. J. McMurphy, *J. Am. Chem. Soc.* **86**, 4624 (1964).



The fact that such a rearrangement is not possible for steric reasons in 2-epi isomers forces the degradation in a different direction. The fragmentation shown by the example of quebrachidine<sup>157, 158</sup> may be visualized as follows: (266)→[267]→[268]→[269]:



The ajmaline fragmentation pattern is also considerably altered if the OH group in position 17 is substituted by a carbonyl group.<sup>156, 157</sup>

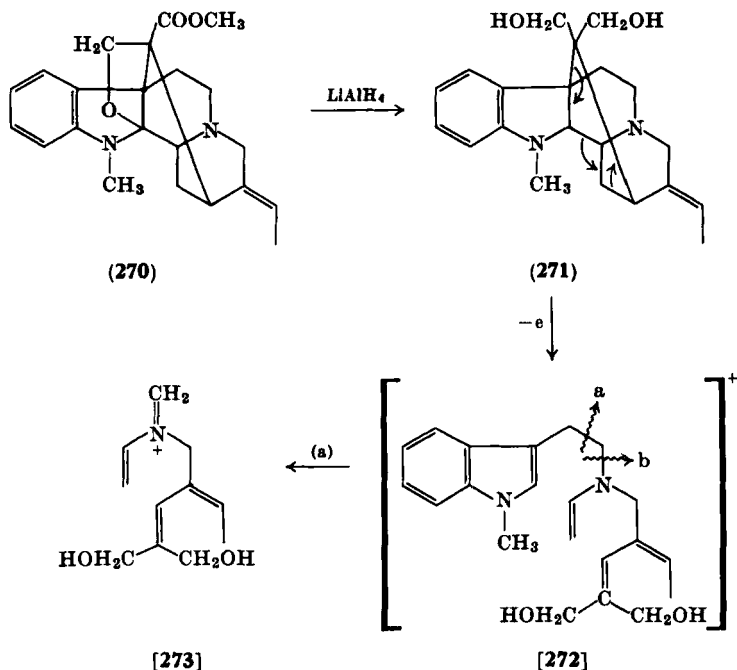
The spectra of the  $\psi$ -akuammigine-type alkaloids (270) show peaks which indicate merely the easy loss of one molecule of formaldehyde, followed by the expulsion of a carbomethoxy group, thus hindering the detection of special structure features.<sup>159, 160</sup> However, the fragmentation pattern becomes richer in characteristic fragments if

<sup>158</sup> M. Gorman, A. L. Burlingame, and K. Biemann, *Tetrahedron Letters* p. 39 (1963).

<sup>159</sup> L. Olivier, J. Lévy, J. LeMen, M. M. Janot, C. Djerassi, H. Budzikiewicz, J. M. Wilson, and L. J. Durham, *Bull. Soc. Chim. France* p. 646 (1963).

<sup>160</sup> A. Z. Britten, P. N. Edwards, J. A. Joule, G. F. Smith, and G. Spittler, *Chem. Ind. (London)*, p. 1120 (1963).

compounds of type (270) are reduced to the corresponding alcohols (271). These are readily cleaved to an intermediate [272]. Subsequent fission at bond "a" or "b" produces indole fragments of mass 144, 157, and 158 (if the charge is localized in the indole part of the molecule), and by cleavage at "a" (if the charge is localized in the piperidine part) a fragment of mass 196 [273] is formed. The latter easily loses water, or formaldehyde, or both.



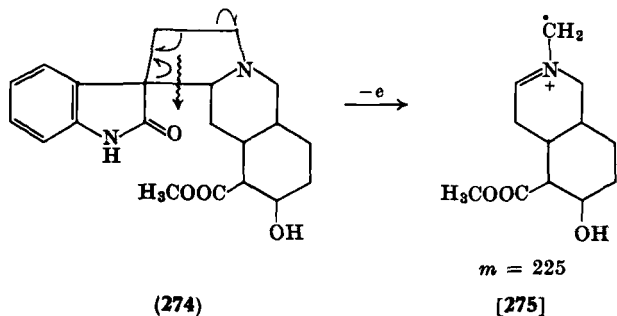
The mass spectra of  $\psi$ -akuammigol (271) and related compounds proved very helpful in determining the structure of  $\psi$ -akuammigine and derivatives.<sup>159, 160</sup> The proposed formula of picraline<sup>160</sup> was shown by chemical and mass spectrometric arguments to be untenable and was revised.<sup>161</sup> Mass spectrometry also aided in the structure determination of the related alkaloid aspidodasycarpine.<sup>162</sup>

n. *Oxindole and Pseudoindoxyl Alkaloids*. Oxindole alkaloids, e.g.,

<sup>161</sup> A. Z. Britten, G. F. Smith, and G. Spiteller, *Chem. Ind. (London)*, p. 1492 (1963).

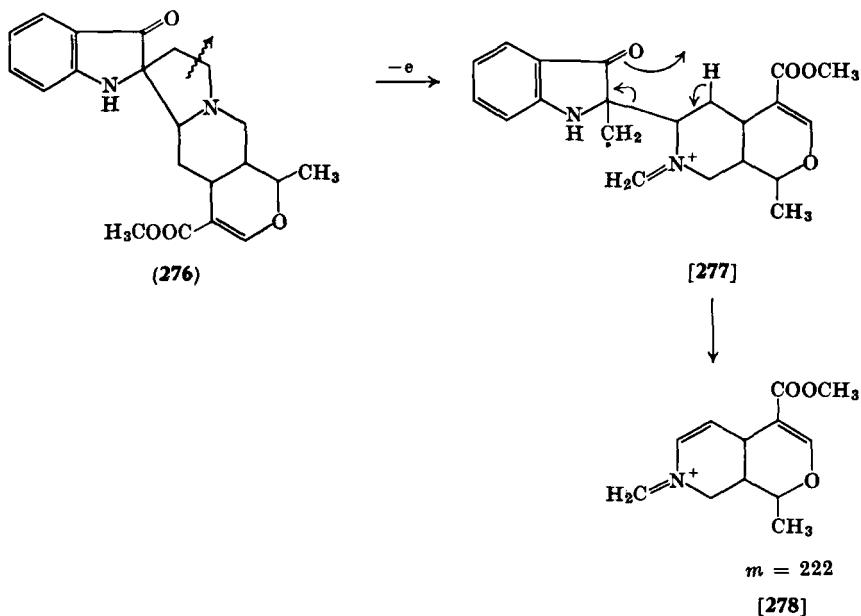
<sup>162</sup> M. Ohashi, J. A. Joule, and C. Djerassi, *Tetrahedron Letters* p. 3899 (1964).

yohimbine oxindole B (274), are characterized in their mass spectra by a very important fragment of mass 225. It is formed by fissions in the indicated way, (274)→[275]<sup>93</sup>:



This fragmentation behavior of oxindole alkaloids was used for the structural elucidation of carapanaubine<sup>93</sup> and stipulatine.<sup>163</sup>

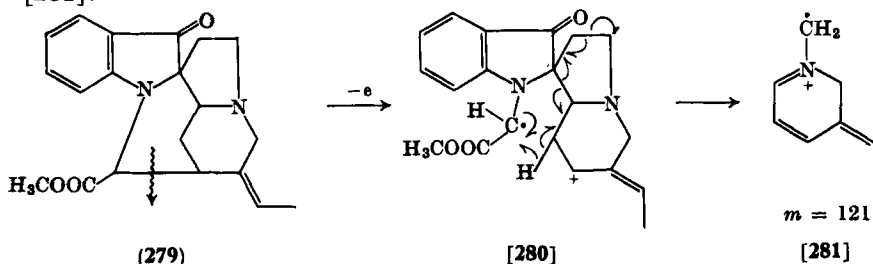
The main degradation process in pseudoindoxyls<sup>164</sup> involves a McLafferty rearrangement, (276)→[277]→[278]:



<sup>163</sup> J. B. Hendrickson and J. J. Sims, *Tetrahedron Letters* p. 929 (1963).

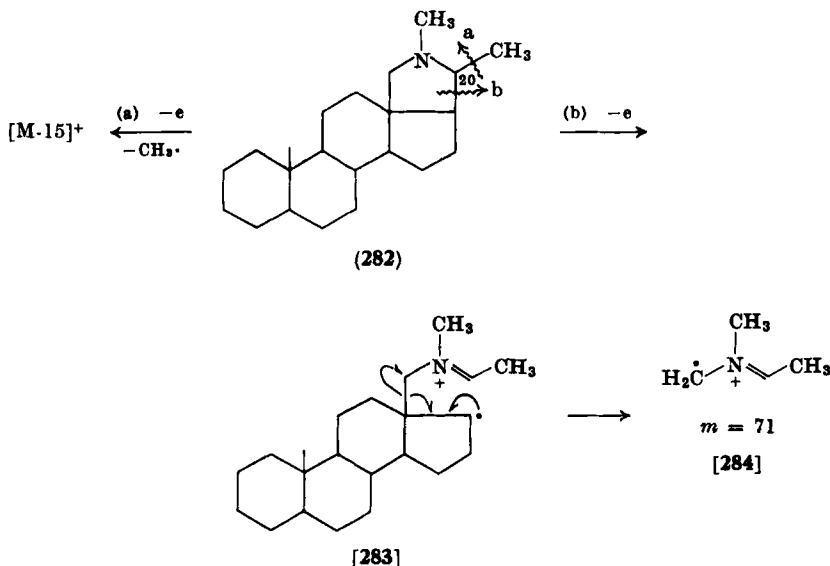
<sup>164</sup> N. Finch, I. Hsiu-Chu Hsu, W. I. Taylor, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.* **86**, 2620 (1964).

In pseudoindoxyls derived from the mavacurine-pleiocarpamine class a different type of fragmentation was observed,<sup>103</sup> (279) → [280] → [281]:



The driving force for this different cleavage reaction, in comparison with that in pseudoindoxyls of type (276), seems to arise from the ethylidene double bond.

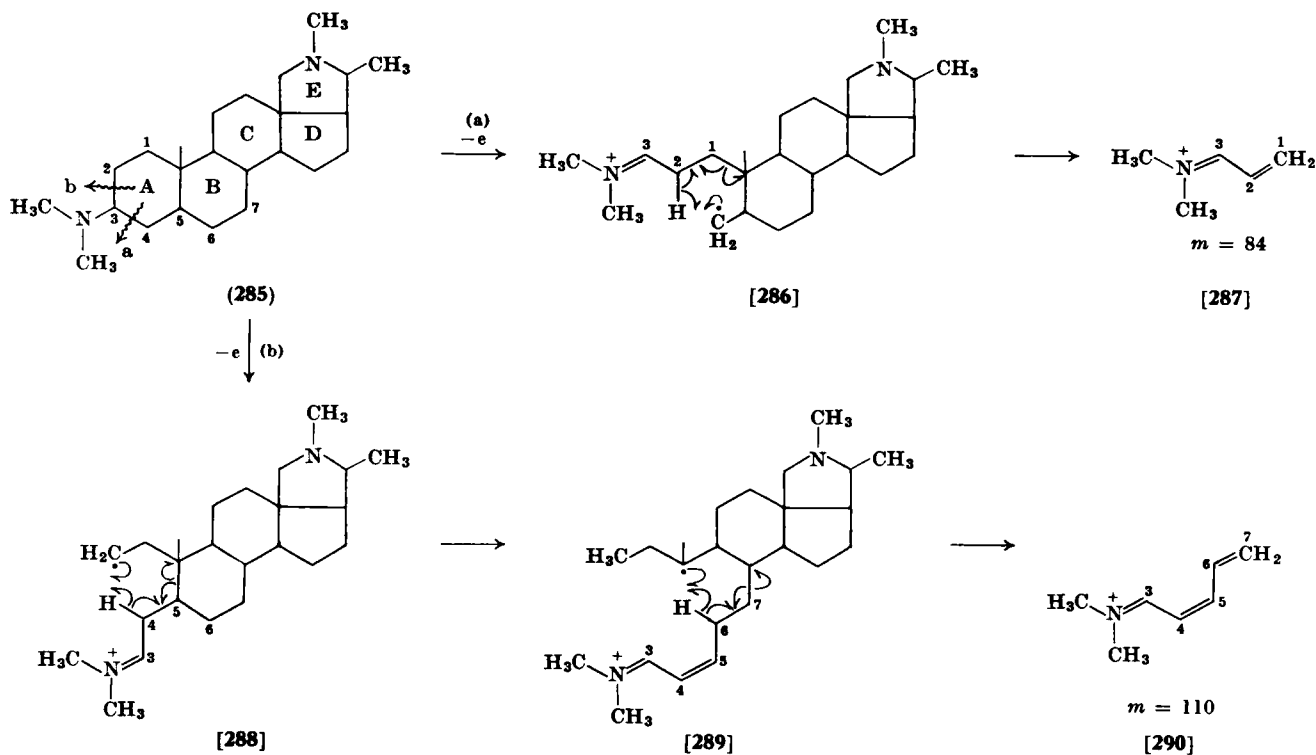
o. *Steroidal Alkaloids*. The mass spectra of different classes of steroidal alkaloids were reviewed only recently.<sup>52, 165</sup> They usually contain only a few fragments of high intensity.<sup>166, 167</sup>



<sup>165</sup> H. Budzikiewicz, *Tetrahedron* **20**, 2267 (1964).

<sup>166</sup> W. Vetter, P. Longevialle, F. Khuong-Huu-Laine, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. France* p. 1324 (1963).

<sup>167</sup> L. Dolejš, V. Hanuš, V. Černý, and F. Šorm, *Collection Czech. Chem. Commun.* **28**, 1584 (1963).

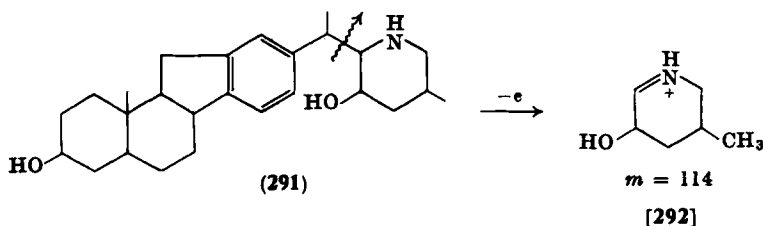


In conanine-type alkaloids (282) the most important cleavage reactions involve either the loss of the methyl group at C-20 or the production of a fragment of mass 71, (282)→[283]→[284].<sup>166</sup>

In dihydroconessine (285) the nitrogen at C-3 competes successfully for the positive charge with the nitrogen of ring E. Therefore, besides the fragments of mass 71 and M-15, two other prominent fragments of mass 84 and 110 are produced,<sup>166, 167</sup> (285)→[286]→[287], (285)→[288]→[289]→[290].

The fission mechanisms assigned were proved by labeling.<sup>168</sup> The proposed structure of  $\alpha$ -hydroxyconessine was confirmed by mass spectrometry<sup>169</sup> and several steroidal alkaloids occurring in *Holarrhena* could be detected and identified.<sup>170</sup>

Members of the veratramine class show the most important fragment at mass 114,<sup>165</sup> (291)→[292].



A fragment of the same molecular formula as [292] is reported to be the main degradation product of solanocapsine and solasodine<sup>165</sup> which have quite different skeletons. So the occurrence of a fragment of mass 114 is not specific for the veratramine group only.

If the nitrogen atom is located as in solanidine (293), a very prominent fragment at mass 150 is found, (293)→[294]→[295].<sup>165</sup>

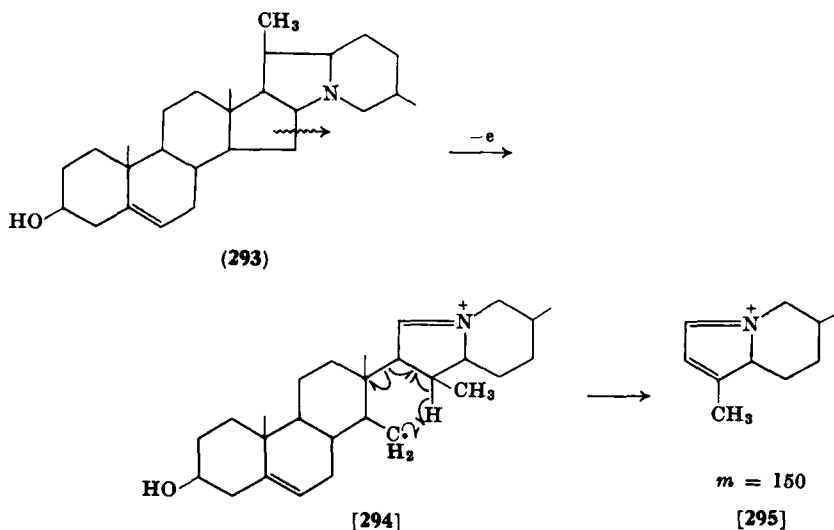
## 2. Purines and Related Compounds

The tendency to fragmentation is rather low in purines, e.g., caffeine (296). Main cleavage processes occur in ring B by expulsion of methylisocyanate and CO, either in one or two steps. The resulting

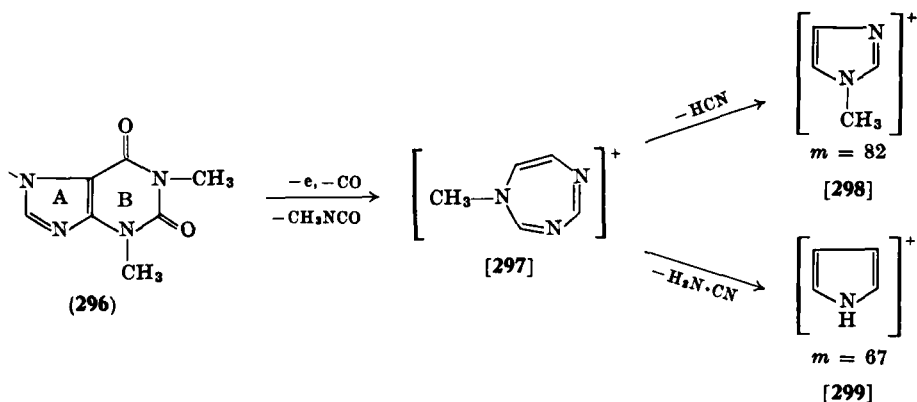
<sup>168</sup> Z. Pelah, M. A. Kielczewski, J. M. Wilson, M. Ohashi, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.* **85**, 2470 (1963).

<sup>169</sup> R. Goutarel, M. Conreur, and J. Parello, *Bull. Soc. Chim. France* p. 2401 (1963).

<sup>170</sup> V. Černý, L. Dolejš, and F. Šorm, *Collection Czech. Chem. Commun.* **29**, 1591 (1964).



ion is thought to have a tropylium-like structure [297]. It is further degraded by expulsion of one or two molecules of HCN or cyanamide, <sup>171</sup> [297] → [298], [297] → [299]:



Very similar degradation routes are reported for pyrimidines.<sup>171a</sup>

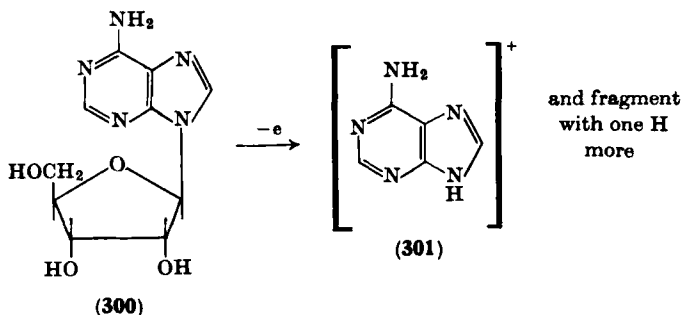
A preliminary report on the mass spectra of nucleosides has been given by Biemann.<sup>172</sup> Key fragments are produced by rupture of the

<sup>171</sup> G. Spiteller and M. Spiteller-Friedmann, *Monatsh.* **93**, 632 (1962).

<sup>171a</sup> T. Goto, A. Tatematsu, and S. Matsuura, *J. Org. Chem.* **30**, 1844 (1965).

<sup>172</sup> K. Biemann and J. A. McCloskey, *J. Am. Chem. Soc.* **84**, 2005 (1962).

bonds linking the purine or pyrimidine part with the sugar moiety, as shown in the case of adenosine (300). In this cleavage reaction, rearrangement of one or two hydrogens from hydroxyls of the sugar to the base is involved. The intensity of the peak corresponding to the sugar moiety varies considerably with the kind of nucleoside investigated, (300)→[301]:



### 3. Porphyrins

Some spectra of metal complexes of porphyrins have been published.<sup>173,174</sup> Besides extremely intense parent peaks, they show mainly doubly charged molecular ions. In alkyl-substituted porphyrins the loss of the side chain is rather favored, probably with cleavage of benzylic-type bonds.<sup>173</sup>

The reported spectrum of copper phthalocyanine is very much contaminated with that of phthalonitrile, which is produced during the evaporation by thermal cracking.<sup>175</sup>

### 4. Metabolic Products

A mass spectrometric investigation<sup>176</sup> proved that sporidesmin B (302) has the same carbon skeleton as sporidesmin, and differs only in the absence of a hydroxyl group attached to ring C. Key

<sup>173</sup> J. H. Beynon, R. A. Saunders, and A. E. Williams, *Appl. Spectr.* **17**, 63 (1963).

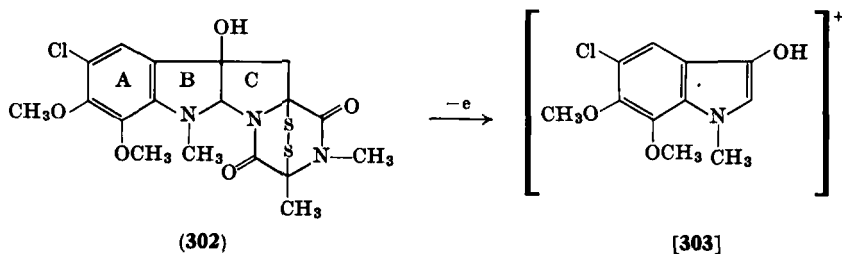
<sup>174</sup> A. Hood, in "Mass Spectrometry of Organic Ions" (F. W. McLafferty), p. 603. Pergamon Press, Oxford, 1963.

<sup>175</sup> H. C. Hill and R. I. Reed, *Tetrahedron* **20**, 1359 (1964).

<sup>176</sup> J. S. Shannon, *Tetrahedron Letters* p. 801 (1963).

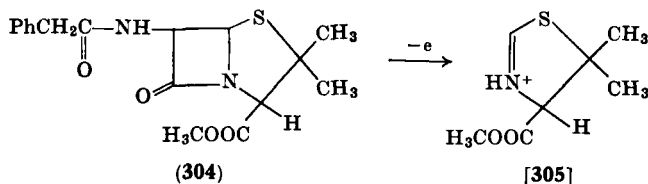


fragments are produced by rupture of ring C, (302)→[303], and by loss of S<sub>2</sub>:



The rather complicated mechanisms deduced for the production of the various ions require further investigation.

A mass spectrometric investigation of methyl esters of penicillins and some derivatives thereof was carried out with the aid of a high-resolution instrument.<sup>177</sup> The main degradation reaction of penicillin proceeds with cleavage of the β-lactam ring and hydrogen rearrangement to the ion [305]: (304)→[305]. A structure assignment to fragments of minor importance could be achieved by high resolution.



Mass spectrometry may also aid in the structure determination of derivatives of cephalosporine-C.<sup>177a</sup>

### 5. Sulfonamides

The mass spectra of sulfonamides derived from heterocyclic bases, e.g., sulfathiazole (306) (Fig. 10), show mainly fragments corresponding to a stepwise degradation of the sulfanilamide moiety, (306)→[307]→[308]→[309]→[49].<sup>178</sup>

The expulsion of SO<sub>2</sub> is a favored process if the amide nitrogen is connected to a carbon having a partial positive charge. The elimination

<sup>177</sup> W. Richter and K. Biemann, *Monatsh.* **95**, 766 (1964).

<sup>177a</sup> W. Richter and K. Biemann, *Monatsh.* **96**, 484 (1965).

<sup>178</sup> G. Spitteller and R. Kaschnitz, *Monatsh.* **94**, 964 (1963).



#### IV. Mass Spectrometric Investigation of Mixtures

The mass spectrum of a mixture is the sum of the intensity contributions of the individual compounds; the spectrum of one compound of this mixture does not influence the spectrum of another. If a mixture consists of compounds of different molecular weights, and if the molecular ions of these compounds are not too unstable, they can easily be recognized in the mass spectrum using the so-called low-voltage technique by keeping the energy of the bombarding electrons just above the ionization threshold, so that the energy is sufficient to produce the molecular ions but too low to cleave them further into fragments.<sup>179-181</sup>

This technique is especially useful in the detection of homologs of alkyl-substituted heterocyclic compounds, which are often produced by drastic degradation operations (Zn dust distillation, Se dehydrogenation, KOH fusion) of complicated natural products, as was shown by establishing the structural formulas of quebrachamine<sup>104</sup> and aspidospermatine.<sup>122</sup> The type of heterocyclic compound may easily be deduced from the molecular weights. Thus for instance pyridines show molecular weights of  $79 + (n \times 14)$ , indoles of  $117 + (n \times 14)$ , quinolines and isoquinolines of  $129 + (n \times 14)$ , and carbazoles of  $167 + (n \times 14)$  (see Biemann,<sup>10</sup> p. 301). The degradation operations could be performed on a scale of a few milligrams.<sup>104, 122</sup>

Mass spectrometry proved very useful for the preliminary examination of raw drugs obtained from plant material.<sup>95, 96, 122</sup> Usually, the low-voltage technique affords the molecular weights of the components of the mixture. In the alkaloid field especially key fragments often enable the assignment of the skeletal type of the investigated materials.<sup>91, 95, 122, 138</sup> Separation by gas chromatography<sup>101, 104, 122, 123</sup> or column chromatography,<sup>95, 96, 122, 138</sup> with subsequent investigation of the fractions by mass spectrometry, permits the detection of minor compounds and the deduction of their structures in amounts of the order of 1 mg, which is impossible by other methods.

In some cases it is even possible to deduce structures of unknown compounds without isolating them from a mixture. The spectrum of the crude mixture gives the molecular weight of the compounds present. If they are members of the same skeletal type, chemical

<sup>179</sup> F. H. Field and S. H. Hastings, *Anal. Chem.* **28**, 1248 (1956).

<sup>180</sup> G. L. Kearns, N. Maranovski, and G. F. Crable, *Anal. Chem.* **31**, 1646 (1959).

<sup>181</sup> H. E. Lumpkin, *Anal. Chem.* **30**, 321 (1958).

reactions can be carried out on the mixture and the reaction products may be investigated again without any purification. From the change in the peaks of the molecular ions and the key fragments it can often quickly be seen what had happened to the mixture during the reaction on a milligram scale. This type of investigation was used recently to establish the structure of a mixture of eight very similar alkaloids extracted from the bark of *Aspidosperma oblongum* A. DC.<sup>95, 96</sup> The formulas of these alkaloids, established with only 30 mg of mixture, were confirmed independently.<sup>182</sup>

<sup>182</sup> J. P. Kutney and R. T. Brown, *Tetrahedron Letters* p. 1815 (1963).

# The Development of the Chemistry of Furans, 1952-1963\*

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\* Translated by B. Ternai, University of East Anglia, Norwich, England.

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## I. Introduction

A comprehensive and almost complete monograph on furan compounds by A. P. Dunlop and F. N. Peters<sup>1</sup> was published in 1953. The chapter on furans by R. C. Elderfield and T. N. Dodd, Jr., in Elderfield's "Heterocyclic Compounds," Vol. I, was completed in 1950. Short summaries by C.-H. Schmidt<sup>2,3</sup> covered mostly the hydrofurans. It seemed reasonable to extend the work of Dunlop and Peters by summarizing new developments in the field once again. However, limited space prevents us from considering all the work which has been carried out on the furan system. *We shall consider here only those publications which are concerned with either the synthesis or the reactions of simple furan rings.* Accordingly, no work on condensed furans, like benzofuran, will be reviewed. Furthermore, we shall not (with very few exceptions) refer to the reactions of the side chains of furan derivatives, provided these reactions do not involve the furan ring itself. Nitrofuran derivatives have been exhaustively studied in recent years, as they are interesting both biologically and pharmacologically, and they will not be considered here. We further exclude from our discussion all di- and tetrahydrofurans, but make an exception with the keto forms of 3-hydroxyfurans. Naturally occurring compounds which contain furan rings are collected in a table in Section X, but they are not discussed in detail. It was originally intended that a summary of physico-chemical data of furan rings should be included, but lack of space caused us to relinquish the idea. In any case, the UV, IR, and NMR data for these compounds is

<sup>1</sup> A. P. Dunlop and F. N. Peters, "The Furans." Reinhold, New York, 1953.

<sup>2</sup> C.-H. Schmidt, *Angew. Chem.* **67**, 317 (1955).

<sup>3</sup> C.-H. Schmidt, *Angew. Chem.* **68**, 175 (1956).

adequately reviewed in A. R. Katritzky's "Physical Methods in Heterocyclic Chemistry," Vol. II.<sup>4</sup>

We are aware that this review is somewhat abbreviated in certain fields, while in others it is rather extensive. This reflects not only our personal preferences, but the fact that we have had to depend on abstracts for some of our information, due to language difficulties, especially in the case of original work reported in Japanese and Russian. We would be pleased to hear from anyone whose work has not been reported in this review. The literature is reviewed to the end of 1963, but a few selected references are made to work which has been carried out in 1964.

In spite of the above-mentioned limitations we hope to illustrate the remarkable diversity of the chemistry of furans and to show that there are still many possibilities for further investigation.

## II. Syntheses of the Furan Ring

### A. FROM MONOSACCHARIDES

The formation of furfural from pentoses, of 5-methylfurfural from methylpentoses, and of 5-hydroxymethylfurfural from hexoses under acidic conditions has long been known.<sup>1</sup> There are only a few more recent investigations to be mentioned.

Acid-catalyzed dehydration of aldoses and ketoses yields furan derivatives in 40–80% yield. Recently the reaction has been carried out in an organic solvent, e.g., dioxan or triethylene glycol,<sup>5</sup> or with I<sub>2</sub> in dimethylformamide<sup>6</sup> at 100°. Often D-fructose is employed as starting material. This ketose gives glucose via an enediol, which yields 5-hydroxymethylfurfural or its O-acyl derivative by dehydration.<sup>7–10</sup>

D-Glucal smoothly yields 2-methoxymethyl-5-hydroxymethylfuran with methanolic hydrochloric acid<sup>11</sup>:

<sup>4</sup> S. F. Mason, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. 2, p. 1. Academic Press, New York, 1963; A. R. Katritzky and A. P. Ambler, *ibid.* p. 165; R. F. M. White, *ibid.* p. 103.

<sup>5</sup> R. A. Hales, J. W. Le Maistre, and G. O. Orth, U.S. Patent 3,071,599 (1963); see *Chem. Abstr.* **59**, 576 (1963).

<sup>6</sup> T. G. Bonner, E. J. Bourne, and M. Ruskiewicz, *J. Chem. Soc.* p. 787 (1960).

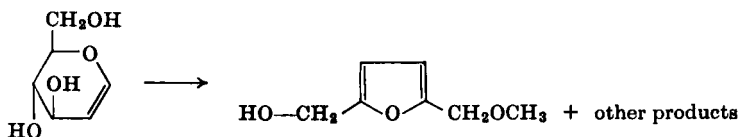
<sup>7</sup> J. Kenner and G. N. Richards, *J. Chem. Soc.* p. 2921 (1956).

<sup>8</sup> E. L. F. J. Anet, *Chem. Ind. (London)*, p. 262 (1962).

<sup>9</sup> A. C. Cope, U.S. Patent 3,079,449 (1963); see *Chem. Abstr.* **59**, 8705 (1963).

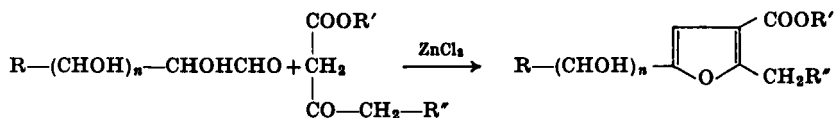
<sup>10</sup> C. J. Moye and Z. S. Krzeminski, *Australian J. Chem.* **16**, 258 (1963).

<sup>11</sup> F. Shafizadeh and M. Stacey, *J. Chem. Soc.* p. 3608 (1952).



It was proved by using labeled compounds that C-1 of xylose becomes the formyl group of furfural.<sup>12</sup> Further analogous preparative methods have been reported,<sup>13, 14</sup> and a pyrolytic preparation of furfural from xylose is known.<sup>15</sup>

The condensation of monosaccharides with  $\beta$ -ketoesters and related compounds:



can be found in a detailed monograph,<sup>16</sup> while other examples are available.<sup>17, 18</sup> These products are used for the synthesis of dehydromuscarones.<sup>19</sup> The condensation of acetoacetic ester with glyoxal to yield methronic acid has long been known, and has recently been reinvestigated.<sup>20</sup> The intermediate is a 3-hydroxy-2,3-dihydrofuran, which yields the furan derivative by an acid-catalyzed elimination of water. Červinka<sup>21</sup> gave a mechanistic explanation for the equally long-known synthesis of methronic acid from sodium succinate and acetoacetic ester.

<sup>12</sup> W. A. Bonner and M. R. Roth, *J. Am. Chem. Soc.* **81**, 5454 (1959).

<sup>13</sup> A. D. Mishin, A. M. Serebrennikova, and T. V. Filatova, *Tr. Inst. Khim. Akad. Nauk SSSR, Ural'sk. Filial* p. 87 (1961); see *Chem. Abstr.* **58**, 11303 (1963).

<sup>14</sup> Belgian Patent 614,724 (1962); see *Chem. Abstr.* **58**, 10172 (1962).

<sup>15</sup> G. Domburgs and V. N. Sergeeva, *Latvijas PSR Zinatnu Akad. Vestis* No. 5, 109 (1960); see *Chem. Abstr.* **55**, 8374 (1961).

<sup>16</sup> F. García González, *Advan. Carbohydrate Chem.* **11**, 97 (1956).

<sup>17</sup> F. García González, F. J. López Aparicio, and M. Ortiz Risso, *Anales Real Soc. Espan. Fis. Quím.* **53B**, 503; see *Chem. Abstr.* **54**, 2305 (1960).

<sup>18</sup> H. H. Szmant and M. L. Estévez, *Mem. Conf. Anual Asoc. Tec. Azúcar. Cuba* **33**, 155 (1959); see *Chem. Abstr.* **55**, 22276 (1961).

<sup>19</sup> R. E. Rosenkranz, K. Allner, R. Good, W. von Philipsborn, and C. H. Eugster, *Helv. Chim. Acta* **46**, 1259 (1963).

<sup>20</sup> M. Selim-Dorgans, M. Selim, and H. Gault, *Compt. Rend.* **244**, 1047 (1957).

<sup>21</sup> O. Červinka, *Chem. Ind. (London)* p. 472 (1961).



## B. DECARBOXYLATION OF FURAN CARBOXYLIC ACIDS

Furan carboxylic acids usually decarboxylate readily, and this method is often used in the laboratory for the preparation of furans. Furan itself can be obtained in good yield from 2-furoic acid in quinoline, with a copper catalyst, while industrial methods employ the catalytic decarbonylation of furfural. Copper powder, copper oxide or copper bronze, or heavy metal oxides,<sup>22</sup> are the best catalysts, in combination with quinoline as solvent and weak base.<sup>23-28</sup> Dann *et al.*<sup>29</sup> decarboxylated 2,5-dimethyl-3-furoic acid in 50% yield using barium hydroxide. 3-Furoic acid, which is difficult to obtain in large quantities, is best prepared by controlled decarboxylation of the easily prepared furan tetracarboxylic acid.

## C. DECARBONYLATION OF FURFURAL

The decarbonylation of furfural to give furan is best carried out at rather high temperatures. The following catalysts have been described: Pd or Pd on charcoal,<sup>30</sup> calcium oxide,<sup>31, 32</sup> zinc and iron chromite,<sup>33</sup> or zinc, chromium, and manganese oxide (from ammonium chromate and manganese nitrate).<sup>34</sup> The optimum reaction temperature with

<sup>22</sup> L. Mészáros, *Acta Univ. Szeged., Acta Phys. Chem.* **6**, 97 (1960); see *Chem. Abstr.* **55**, 25905 (1961).

<sup>23</sup> S. Malinowski, *Roczniki Chem.* **27**, 54 (1953); see *Chem. Abstr.* **48**, 13678 (1954).

<sup>24</sup> D. M. Burness, *J. Org. Chem.* **21**, 102 (1956).

<sup>25</sup> F. Boberg and A. Kieso, *Ann.* **626**, 71 (1959).

<sup>26</sup> B. Bak, J. T. Nielsen, and M. Schottländer, *Acta Chem. Scand.* **16**, 771 (1962).

<sup>27</sup> Z. N. Nazarova, Yu. A. Babaev, and T. N. Natalina, *Zh. Obshch. Khim.* **33**, 1431 (1963); see *Chem. Abstr.* **59**, 11390 (1963).

<sup>28</sup> Ya. L. Gol'dfarb and Ya. L. Danyushevskii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 540 (1963); see *Chem. Abstr.* **59**, 3861 (1963).

<sup>29</sup> O. Dann, H. Distler, and H. Merkel, *Ber.* **85**, 457 (1952).

<sup>30</sup> H. B. Copelin and D. I. Garnett, U.S. Patent 3,007,941 (1959); see *Chem. Abstr.* **56**, 7281 (1962).

<sup>31</sup> G. Noyori *et al.*, Japanese Patent 4,332 (1953); see *Chem. Abstr.* **49**, 4722 (1955).

<sup>32</sup> S. Hillers, *Vopr. Ispol'z. Pentozansoderzh. Syr'ya, Tr. Vses. Soveshch., Riga, 1955*, p. 299 (1958); see *Chem. Abstr.* **53**, 14076 (1959).

<sup>33</sup> L. W. Tyran, U.S. Patent 2,776,981 (1957); see *Chem. Abstr.* **51**, 8143 (1957).

<sup>34</sup> A. Ya. Karmilchicks and S. Hillers, *Vopr. Ispol'z. Pentozansoderzh. Syr'ya Tr. Vses. Soveshch., Riga, 1955* p. 327 (1958); see *Chem. Abstr.* **53**, 15037 (1959).

the latter catalyst is 440–460° and the yield approaches 90%. During the reaction hydrocarbons are absorbed on the surface of the catalyst, and the efficiency falls off after 11 to 12 hours. Regeneration is effected by atmospheric oxygen at 500–550°.

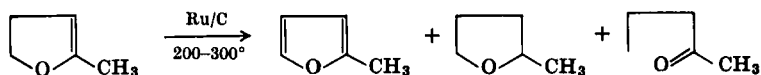
The mechanism of the decarbonylation reaction is not yet known. Vándor<sup>35</sup> suggested that a vapor-phase Cannizzaro reaction takes place when the reaction is carried out with an excess of steam.

## D. FROM DIHYDROFURANS

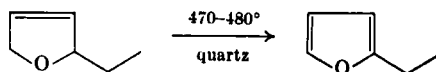
### 1. *By Catalytic Dehydrogenation*

Catalytic dehydrogenation of dihydrofurans is unsatisfactory, as in several cases secondary reactions take place. These are:

- (a) hydrogenation to tetrahydrofuran;
- (b) hydrogenolytic ring opening,<sup>36, 37</sup> e.g.,



Bel'skii *et al.*<sup>38</sup> carried out an evidently more simple dehydrogenation over silica:



### 2. *Via Elimination of Alcohol or Water from Dihydrofurans*

Pyrolysis of 2,5-dialkoxy- or -diacetoxy-2,5-dihydrofurans results in a smooth reaction with the formation of 2-substituted furans.<sup>39, 40</sup>

<sup>35</sup> J. Vándor, *Acta Chim. Acad. Sci. Hung.* **3**, 169 (1953); see *Chem. Abstr.* **48**, 9994 (1954).

<sup>36</sup> N. I. Shuikin, I. F. Bel'skii, and R. A. Karakhanov, *Dokl. Akad. Nauk SSSR* **147**, 119 (1961); see *Chem. Abstr.* **58**, 11304 (1963).

<sup>37</sup> N. I. Shuikin, I. F. Bel'skii, and R. A. Karakhanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 138 (1962); see *Chem. Abstr.* **57**, 12406 (1962).

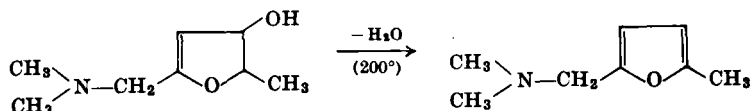
<sup>38</sup> I. F. Bel'skii, N. I. Shuikin, and R. A. Karakhanov, *Dokl. Akad. Nauk SSSR* **132**, 585 (1960); see *Chem. Abstr.* **54**, 24623 (1960).

<sup>39</sup> Kemisk Vaerk Koge, Danish Patent 76,519 (1953); see *Chem. Abstr.* **49**, 1105 (1955).

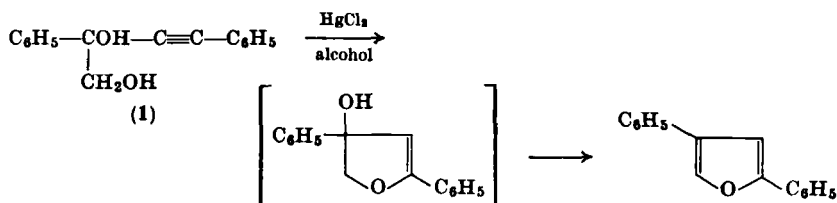
<sup>40</sup> M. P. Cava, C. L. Wilson, and C. J. Williams, *Chem. Ind. (London)* p. 17 (1955).

The reaction will be described in more detail in Section VIII. The dehydration of 2,3-dihydro-3-hydroxyfurans generally proceeds without difficulty

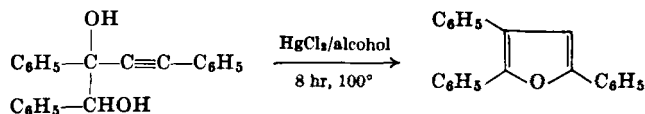
*cis*- and *trans*-4,5-dehydronormuscarine were converted into 2-dimethylaminomethyl-5-methylfuran<sup>41</sup> by heating at 200°:



In the synthesis of 2,4-diphenylfurans from the acetyleneglycol (1), the intermediate was not isolated<sup>42</sup>:



Triphenylfuran is obtained in 85–90% yield from an acetylene-glycol, as a result of an apparently similar ring closure<sup>43</sup>:



#### E. FROM TETRAHYDROFURANS

Gross<sup>44</sup> chlorinated tetrahydrofuran at  $-30$  to  $-40^\circ$  in UV light. Dehydrohalogenation of the product with tertiary amines yielded furan.

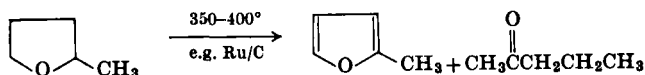
<sup>41</sup> R. Denss, E. Girod, F. Häfliger, and C. H. Eugster, *Helv. Chim. Acta* **42**, 1191 (1959).

<sup>42</sup> L. A. Pavlova, *Zh. Obshch. Khim.* **25**, 1521 (1955); see *Chem. Abstr.* **50**, 4898 (1956).

<sup>43</sup> E. D. Venus-Danilova and V. M. Al'bitskaya, *Zh. Obshch. Khim.* **22**, 816 (1952); see *Chem. Abstr.* **47**, 3266 (1953).

<sup>44</sup> H. Gross, *Angew. Chem.* **72**, 268 (1960).

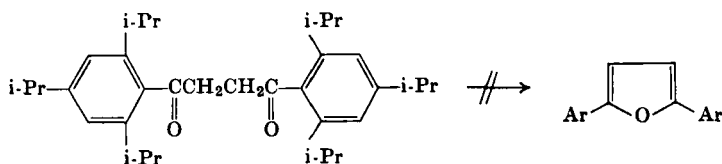
Catalytic dehydrogenation of tetrahydrofurans is more difficult; by-products form because the ring is often ruptured. Thus, the following reaction<sup>45</sup> has a yield of 50–70% of the furan:



The preparation of 3-phenylfuran from 3-hydroxy-3-phenyl-tetrahydrofuran is described by Wynberg.<sup>46</sup> The dehydrogenation was effected by sulfur in dimethylformamide. Sulfur is equally suitable for the preparation of 3,4-diphenylfuran, which is obtained in 25% yield.<sup>47</sup> Potassium ferricyanide has also been successfully employed for the dehydrogenation of 3-carbethoxytetrahydrofuran.<sup>48</sup>

#### F. FROM 1,4-DIKETONES

Dehydration of 1,4-diketones results in cyclization, and this method is often employed for the synthesis of furans. This is feasible in the case of all those 1,4-diketones which are not sterically hindered. Thus, no ring closure occurs with 1,4-bis-(2,4,6-triisopropylphenyl)-1,4-butanedione.<sup>49</sup>



The cyclization is often carried out with sulfuric acid.<sup>50–53</sup> A 1,2-

<sup>45</sup> I. F. Bel'skii, N. I. Shuikin, and R. A. Karakhanov, *Dokl. Akad. Nauk SSSR* **138**, 829 (1961); see *Chem. Abstr.* **55**, 22280 (1961).

<sup>46</sup> H. Wynberg, *J. Am. Chem. Soc.* **80**, 364 (1958).

<sup>47</sup> D. G. Farnum and M. Burr, *J. Org. Chem.* **28**, 1387 (1963).

<sup>48</sup> A. Ghosh and C. R. Raha, *J. Indian Chem. Soc.* **31**, 461 (1954); see *Chem. Abstr.* **49**, 13203 (1955).

<sup>49</sup> G. Nowlin, *J. Am. Chem. Soc.* **72**, 5754 (1950).

<sup>50</sup> E. C. Kornfeld and R. G. Jones, *J. Org. Chem.* **19**, 1671 (1954).

<sup>51</sup> R. G. Jones, *J. Am. Chem. Soc.* **77**, 4069 (1955).

<sup>52</sup> O. Dann, E. Pietschmann, and W. Dimmling, *Arch. Pharm.* **292**, 508 (1959).

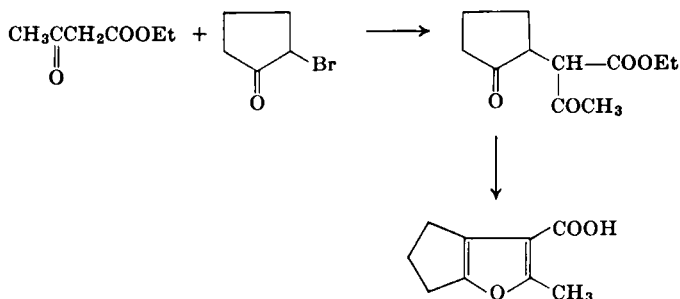
<sup>53</sup> I. V. Machinskaya, G. P. Smirnova, and V. A. Barkhash, *Zh. Obshch. Khim.* **32**, 1248 (1962); see *Chem. Abstr.* **58**, 3377 (1963).

diacetylene was cyclized to a furylacrylic acid derivative by hydrochloric acid.<sup>54</sup> Polyphosphoric acid,<sup>49</sup> phosphorus trichloride,<sup>55</sup> zinc chloride,<sup>56</sup> and dimethyl sulfoxide<sup>57</sup> have found application. The last ensures that the reaction conditions are strictly neutral, and apparently phosphoric esters serve the same purpose.<sup>58</sup>

A base-catalyzed cyclization was described by Acheson and Robinson.<sup>59</sup> They treated  $\alpha$ -acetyllevulic ester with *cold* sodium ethoxide, and obtained 3-carbethoxy-2,5-dimethylfuran in 83% yield.

A few examples may be taken from recent work:

Condensation of acetoacetic ester with  $\alpha$ -bromocyclopentanone, followed by ring closure with cold sulfuric acid, gave 2-methyl-3-carboxy-4,5-trimethylenefuran in 41% yield<sup>53</sup>:



Dien and Lutz<sup>60</sup> observed an unexpected effect on the course of the reaction of **2** by variation of the acidic catalyst. The reaction with  $\text{SnCl}_2$  or  $\text{SnCl}_4/\text{HCl}$  gave rise to 80% (**3**) and 13% (**4**), while with  $\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$ , 72% (**4**) and 9% (**3**) were obtained:

<sup>54</sup> I. Ernest and J. Staněk, Czech. Patent 88,760 (1959); see *Chem. Abstr.* **54**, 8849 (1960).

<sup>55</sup> R. E. Lutz and W. J. Welstead, *J. Am. Chem. Soc.* **85**, 755 (1963).

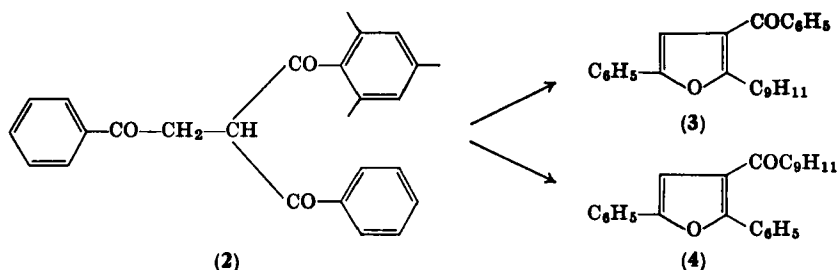
<sup>56</sup> R. Gaertner and R. G. Tonkyn, *J. Am. Chem. Soc.* **73**, 5872 (1951).

<sup>57</sup> V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.* **29**, 123 (1964).

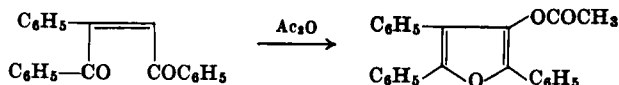
<sup>58</sup> T. Mukaiyama and T. Hata, *Bull. Chem. Soc. Japan* **34**, 99 (1961).

<sup>59</sup> R. M. Acheson and R. Robinson, *J. Chem. Soc.* p. 1127 (1952).

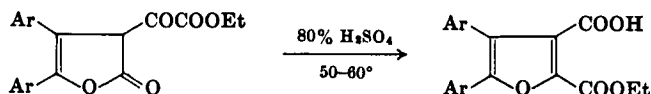
<sup>60</sup> C. K. Dien and R. E. Lutz, *J. Org. Chem.* **21**, 1096 (1956).



The cyclization of a *cis*-dibenzoylphenylethylene in acetic anhydride resulted in the formation of 2,4,5-triphenyl-3-acetoxymfuran<sup>61</sup>:



Vardanyan *et al.*<sup>62</sup> converted a number of 1,2-diaroylthylenes to 2,5-diarylfurans with SnCl<sub>2</sub>/HCl. Analogous to these cyclizations are the reactions on  $\alpha$ -oxalyl- $\gamma$ -lactones,<sup>63</sup>



and  $\alpha,\beta$ -unsaturated  $\alpha$ -acyl- $\gamma$ -lactones,<sup>64</sup> which are readily prepared from diketene. Other examples for 1,4-diketones are available.<sup>29, 65</sup>

Recently a great deal of attention has been paid to ring closure of 1,4-dialdehydes. This is best carried out on the more accessible acetal form, which is exemplified in the work of Kornfeld and Jones<sup>50</sup> on the new synthesis of furan-3,4-dicarboxylic acid. The ester is obtained in 70% yield from 2-formylsuccinic acid, which, after conversion to the acetal, is again formylated and finally cyclized to the product.

Clauson-Kaas suggested a variation of this method.<sup>66</sup> *cis*-2-Butene-1,4-diol is oxidized by chromic acid to the monoaldehyde, which is

<sup>61</sup> R. E. Lutz and C. R. Bauer, *J. Org. Chem.* **19**, 324 (1954).

<sup>62</sup> S. A. Vardanyan, A. G. Vardanyan, and S. P. Khrlakyan, *Zh. Obshch. Khim.* **32**, 1195 (1962); see *Chem. Abstr.* **58**, 1422 (1963).

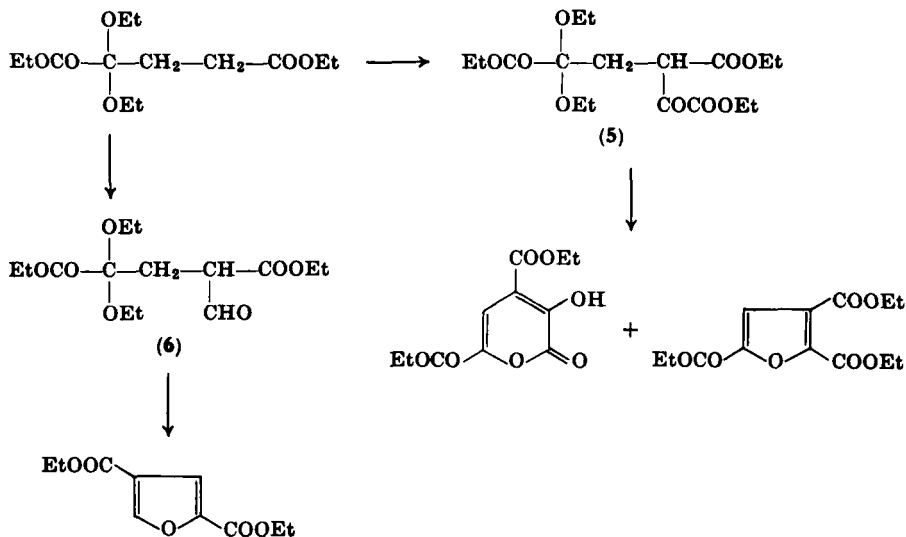
<sup>63</sup> F. G. Baddar and S. Sherif, *J. Chem. Soc.* p. 707 (1961).

<sup>64</sup> R. N. Lacey, *J. Chem. Soc.* p. 822 (1954).

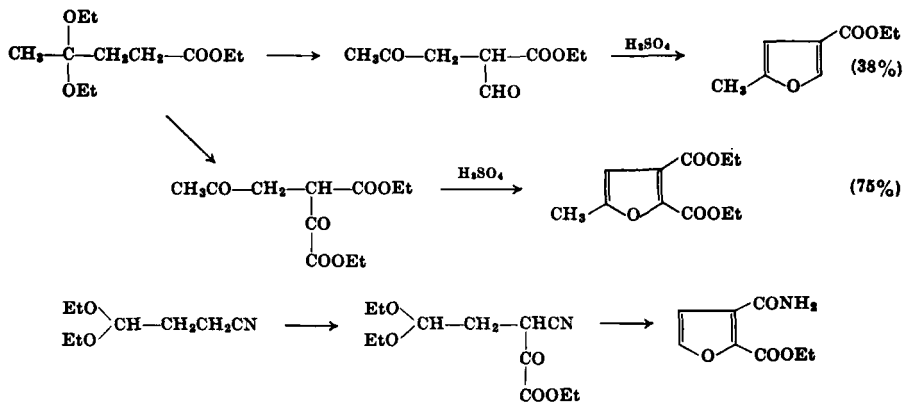
<sup>65</sup> P. S. Bailey, G. Nowlin, and H. W. Bost, *J. Am. Chem. Soc.* **73**, 4078 (1951).

<sup>66</sup> N. Clauson-Kaas, *Acta Chem. Scand.* **15**, 1177 (1961).

cyclized to furan in 62% yield with loss of water. The conversion of ethyl 2,2-diethoxy-4-ethoxalylglutarate (5) and of ethyl 2,2-diethoxy-4-formylglutarate (6) are analogous reactions:



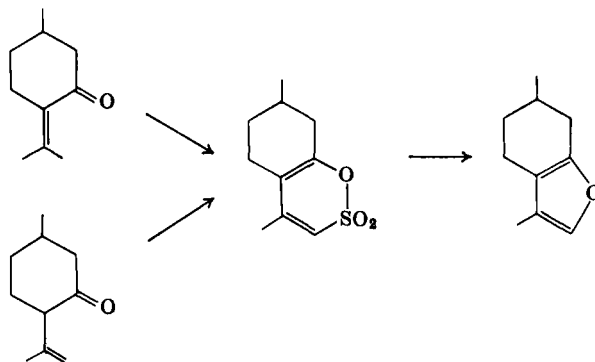
When sulfuric acid is used in the cyclization of 5, an  $\alpha$ -pyrone is the main product, being formed in 71% yield, with small amounts of furan-2,3,5-tricarboxylic ester. Cyclizations of the formyl derivative are more satisfactory.<sup>67</sup> From ethyl levulate and 4,4-diethoxybutyronitrile<sup>51</sup> products were obtained as follows:



<sup>67</sup> R. G. Jones, *J. Am. Chem. Soc.* **77**, 4074 (1955).

G. FROM  $\delta$ -SULTONES

This work was apparently initiated by Treibs,<sup>68</sup> who converted pulegone and isopulegone into  $\delta$ -sultones using a mixture of sulfuric acid and acetic anhydride. Pyrolytic elimination of sulfur dioxide yields menthofuran:



This reaction was recently used by Fétizon and Baranger for the synthesis of tetramethylfuran.<sup>69</sup> In a similar way 2,3,4-trimethylfuran is obtained,<sup>70</sup> and 2,4-dimethylfuran is formed in 76% yield from mesityl oxide.<sup>71</sup>

## H. FROM PYRYLIUM SALTS

Pyrylium salts are also suitable for the preparation of furans.<sup>72, 73</sup> Oxidation of these salts by aqueous hydrogen peroxide in the presence of perchloric acid leads to ring contraction, with the formation of furan derivatives. Nenitzescu and Balaban described the following example<sup>72</sup>:

<sup>68</sup> W. Treibs, *Ber.* **70**, 85 (1937).

<sup>69</sup> M. Fétizon and P. Baranger, *Bull. Soc. Chim. France* p. 1311 (1957).

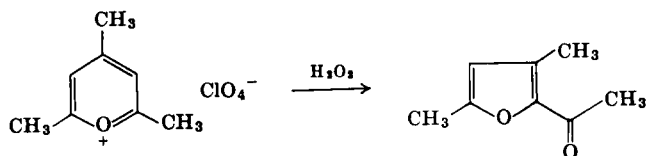
<sup>70</sup> T. Morel and P. E. Verkade, *Rec. Trav. Chim.* **70**, 35 (1951).

<sup>71</sup> Yu. K. Yur'ev, G. Ya. Kondrat'eva, and S. N. Petrov, *Dokl. Akad. Nauk SSSR* **72**, 523 (1950); see *Chem. Abstr.* **45**, 602 (1951).

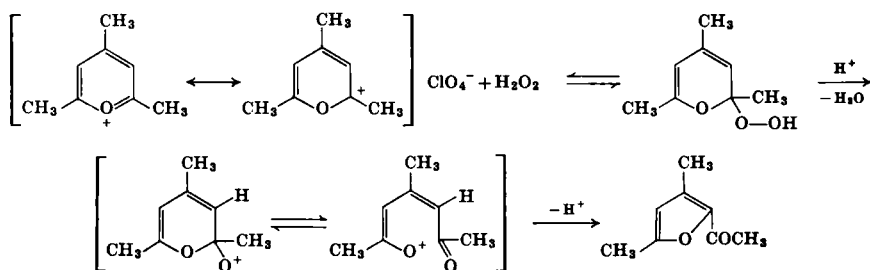
<sup>72</sup> A. T. Balaban and C. D. Nenitzescu, *Ber.* **93**, 599 (1960).

<sup>73</sup> N. I. Shuikin, I. F. Bel'skii, A. T. Balaban, and C. D. Nenitzescu, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 491 (1962); see *Chem. Abstr.* **57**, 15058 (1962).





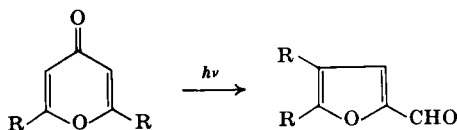
and proposed the following reaction scheme:



### I. FROM PYRONES

The preparation of furans from  $\alpha$ -pyrones has been reported.<sup>74-76</sup> For ring contraction to occur it is necessary that a suitable leaving group should be present in the 3-position. An example is given by Broy and Mayer,<sup>76</sup> where ring opening on 3-hydroxy- $\alpha$ -pyrone occurred in alkaline solution, followed by ring closure to the 2-furoic acid. This reaction was also applied to 3-bromo- $\alpha$ -pyrone.

Yates and Still<sup>77</sup> and Padwa<sup>78</sup> have described the photochemical conversion of certain  $\gamma$ -pyrones into furan-2-aldehydes:



<sup>74</sup> I. El-Sayed El-Kholy and F. K. Rafla, *J. Chem. Soc.* p. 5297 (1962).

<sup>75</sup> B. Bak, J. T. Nielsen, and M. Schottländer, *Acta Chem. Scand.* **16**, 771 (1962).

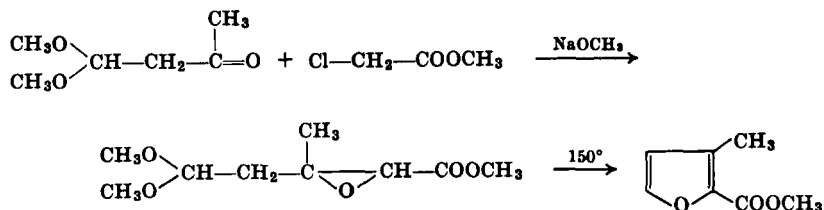
<sup>76</sup> W. Broy and R. Mayer, *Z. Chem.* **3**, 150 (1963); see *Chem. Abstr.* **59**, 7469 (1963).

<sup>77</sup> P. Yates and I. W. J. Still, *J. Am. Chem. Soc.* **85**, 1208 (1963).

<sup>78</sup> A. Padwa, *Tetrahedron Letters* p. 813 (1964).

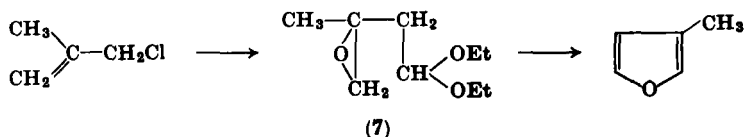
## J. VIA EPOXIDES

Burness<sup>24, 79</sup> prepared 3-methyl-2-carbomethoxyfuran in 55% yield from  $\beta$ -ketobutyral, with rearrangement of the intermediate glycidic ester:

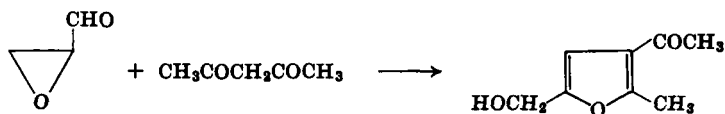


The 3-methylfuran was obtained by subsequent hydrolysis and decarboxylation. 3-Phenylfuran could be prepared analogously via 3-phenyl-2-furoic ester.

Cornforth<sup>80</sup> prepared 3-methylfuran by a somewhat different method. He refluxed 3,4-epoxy-3-methylbutanal diethylacetal (7) with 0.1 *N* sulfuric acid for 3 hours and obtained 3-methylfuran directly in 57% yield:



2-Methyl-3-acetyl-5-hydroxymethylfuran is obtained in high yield (81%) from glycidaldehyde and acetylacetone in glacial acetic acid with piperidine acetate<sup>81</sup>:



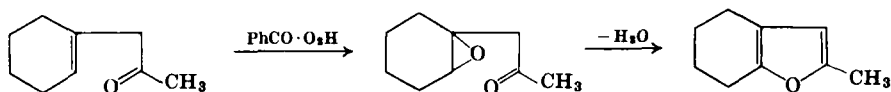
Fritel and Baranger<sup>82</sup> converted cyclohexenylacetone into 2,3-tetramethylenefuran by the action of *p*-toluenesulfonic acid on an intermediate epoxide:

<sup>79</sup> D. M. Burness, U.S. Patent 2,722,295 (1956); see *Chem. Abstr.* **51**, 7424 (1957).

<sup>80</sup> J. W. Cornforth, *J. Chem. Soc.* p. 1310 (1958).

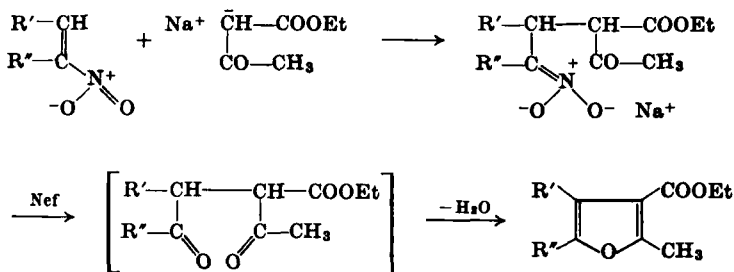
<sup>81</sup> P. H. Williams, G. B. Payne, W. J. Sullivan, and P. R. van Ess, *J. Am. Chem. Soc.* **82**, 4883 (1960).

<sup>82</sup> H. Fritel and P. Baranger, *Compt. Rend.* **241**, 674 (1955).

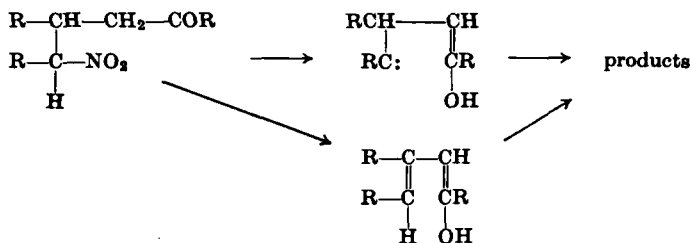


## K. THE NEF REACTION

1-Nitrocyclohexene, 1-nitrocycloheptene, 1-nitrocyclooctene, and  $\beta$ -nitro- $\beta$ -methylstyrene undergo condensation with  $\beta$ -ketoesters in ether, with the formation of *aci*-nitro adducts. On warming, these undergo the Nef reaction. Carbonyl compounds are formed initially, and these by the action of concentrated hydrochloric acid yield 3-furoic esters and their derivatives.<sup>25, 83, 84</sup> The reaction takes place according to the following scheme:



Allen and Happ<sup>85</sup> investigated the thermal reversibility of the Michael adducts. They detected furan derivatives, e.g., triphenyl- and diphenylfuran, in the mass spectra of  $\gamma$ -nitroketones:



<sup>83</sup> F. Boberg and G. R. Schultze, *Ber.* **90**, 1215 (1957).

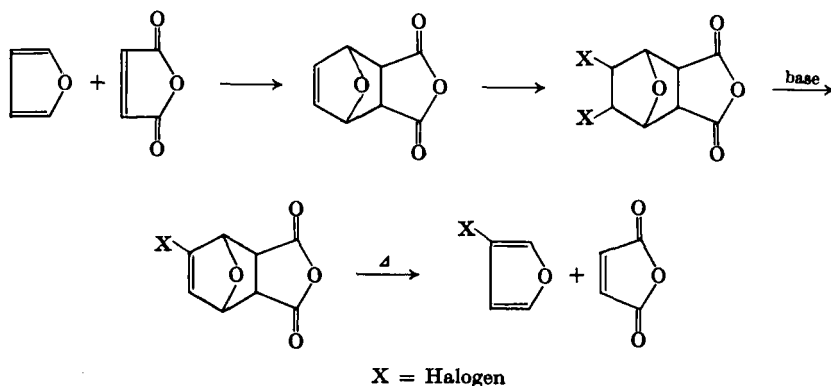
<sup>84</sup> G. R. Schultze and F. Boberg, German Patent 965,408 (1957); see *Chem. Abstr.* **53**, 16150 (1959).

<sup>85</sup> C. F. H. Allen and G. P. Happ, *Can. J. Chem.* **42**, 650 (1964).

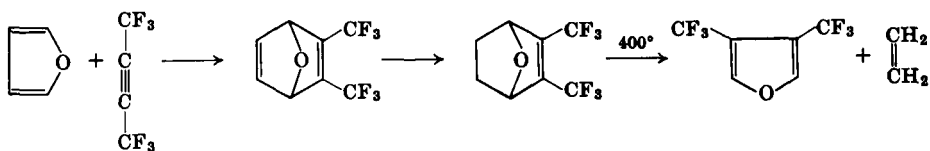
It is not yet established whether a  $\beta$ -elimination of nitrous acid, followed by nucleophilic addition, or formation of a carbene takes place.

### L. FROM DIELS-ALDER ADDUCTS

The Alder-Rickert reaction can be employed in the preparation of 3-substituted furans<sup>86</sup>:



A further example is<sup>87</sup>:



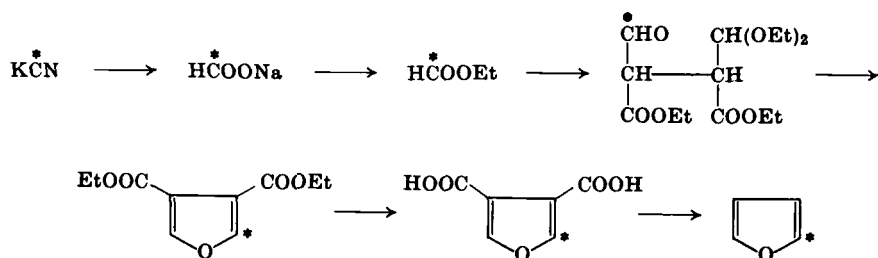
### M. VARIOUS NEW FURAN SYNTHESSES

(a) Bak and co-workers<sup>88</sup> prepared labeled furans with radioactive potassium cyanide as starting material: (1) with C-2 (C-5) labeled—

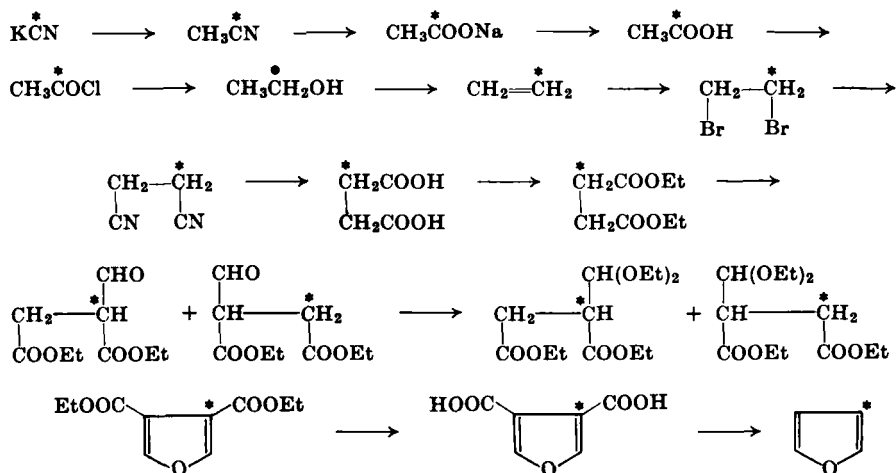
<sup>86</sup> W. W. Lewis, U.S. Patent 2,773,882 (1956); see *Chem. Abstr.* **51**, 8803 (1957).

<sup>87</sup> C. D. Weis, *J. Org. Chem.* **27**, 3693 (1962).

<sup>88</sup> B. Bak, J. T. Nielsen, and M. Schottländer, *Acta Chem. Scand.* **16**, 123 (1962).



(2) with C-3 (C-4) labeled—



(b) Mkryan and Papazyan<sup>89</sup> described a synthesis of 2,5-diphenylfuran from 1,4-diphenyl-1,3-butadiyne. The intermediate is without doubt a 1,4-diketone. The yield was 31%.

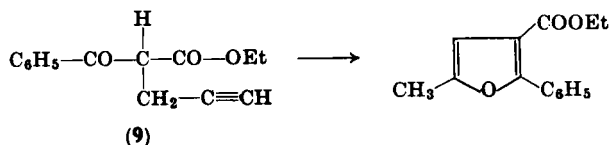
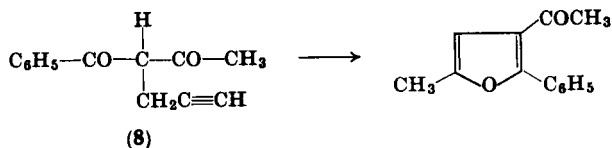
(c) Recently<sup>90</sup> a direct furan synthesis from butadiene was carried out, which involved oxidation with air in the presence of manganous molybdate.

(d) Acetylene diketones of types 8 and 9 can be converted into

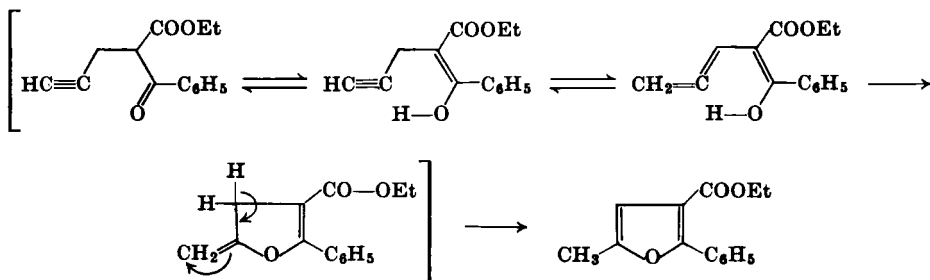
<sup>89</sup> G. M. Mkryan and N. A. Papazyan, *Dokl. Akad. Nauk Arm. SSSR* **21**, 107 (1955); see *Chem. Abstr.* **50**, 9374 (1956).

<sup>90</sup> J. R. Harrison, U.S. Patent 2,900,396 (1959); see *Chem. Abstr.* **54**, 1544 (1960).

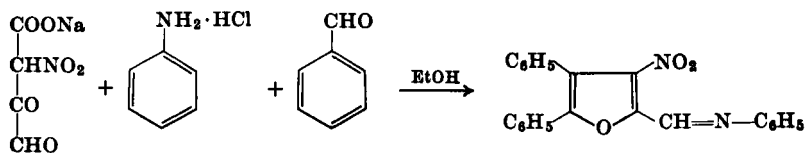
furan derivatives in good yield, by refluxing for a short time with zinc carbonate<sup>91</sup>:



The by-products are pyrans. The reaction probably goes via an allene, with intramolecular addition of the enol to give a dihydrofuran:



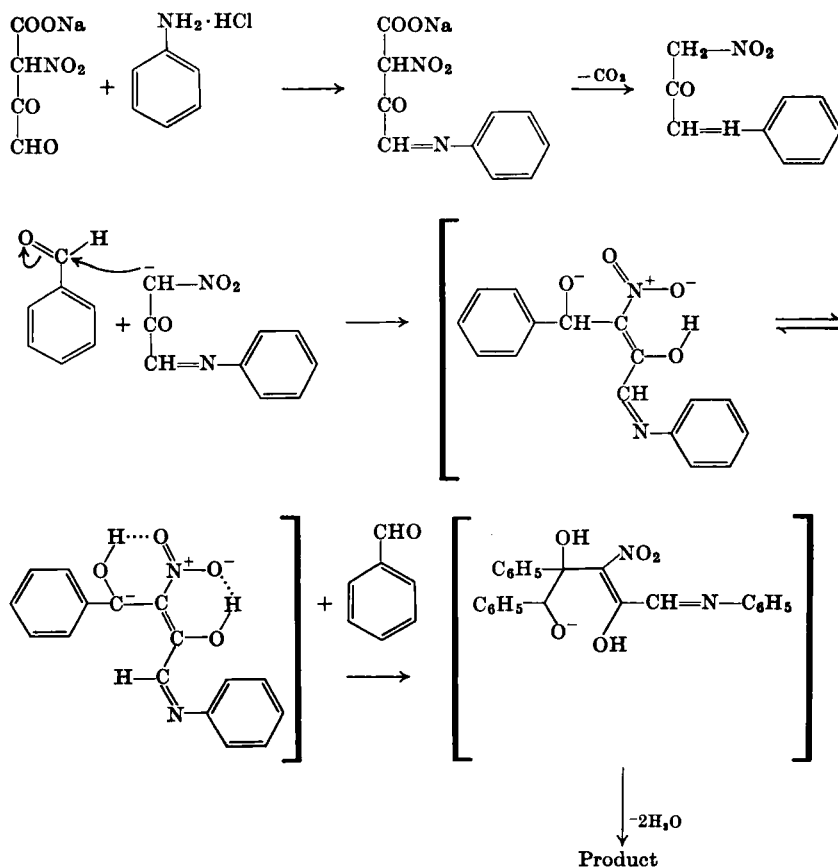
(e) An interesting furan synthesis was described recently by James and Fanta<sup>92</sup>:



<sup>91</sup> K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm.* **295**, 627 (1962).

<sup>92</sup> D. S. James and P. E. Fanta, *J. Org. Chem.* **28**, 390 (1963).

The authors suggest the following mechanism for the reaction:



(f) A noteworthy reaction is the disproportionation of 2-furoic acid in the presence of  $\text{CdI}_2$  to yield furan and furan-2,5-dicarboxylic acid<sup>93</sup>:



The mechanism is probably analogous to the *p*-rearrangement of potassium salicylate or to the Henkel process (phthalic acid  $\rightarrow$  terephthalic acid).

<sup>93</sup> R. Andrisano and A. S. Angeloni, *Ann. Chim. (Rome)* **53**, 1658 (1964).

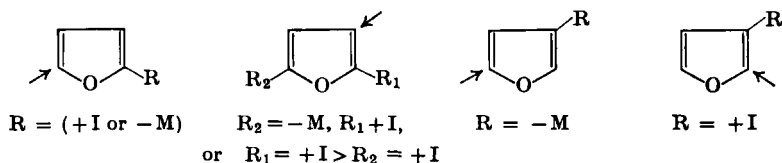
### III. Substitution Reactions of the Furan Ring

#### A. ELECTROPHILIC SUBSTITUTION

Furans undergo electrophilic substitution with exceptional ease, provided that there are no electron-withdrawing groups in the ring. The furan ring is very sensitive to acid attack, and consequently not all of the electrophilic reagents used in aromatic substitution can be employed with it. Recent work has concerned the investigation of reagents and reaction conditions. Most interest has been directed towards the study of the nitrofurans which are biologically active compounds. The furan ring is employed increasingly as a potential carboxyl group which, after electrophilic substitution giving the side chain, is oxidized to the carboxylic acid, e.g., with  $\text{KMnO}_4$ .

The following general rules of electrophilic substitution are based on experimental data:

- (i) substitution occurs preferentially at C-2 and is independent of the nature of the group at C-5;
- (ii) a substituent at C-3 with a  $-M$  effect directs substitution to C-5 and one with a  $+I$  effect to C-2;
- (iii) if both C-2 and C-5 are substituted, the substituent with the stronger  $+I$  effect will direct the entering substituent to the vicinal carbon atom:



Generally, negatively substituted furans require more severe substitution conditions. Presumably these "substitutions" take place initially with 2,5-addition, followed by elimination. Substitution at the 3-position is also expected, but has not been observed when  $\alpha$ -positions are free.

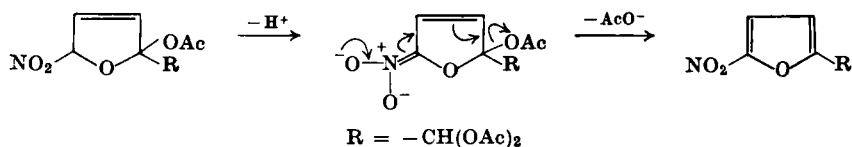
#### 1. Nitration

This is best carried out with a mixture of acetic anhydride and nitric acid (often with the addition of phosphoric or sulfuric acid)



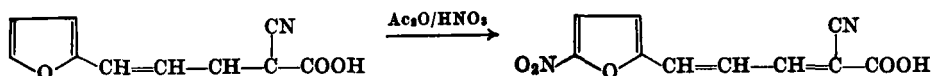
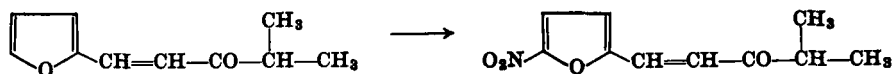
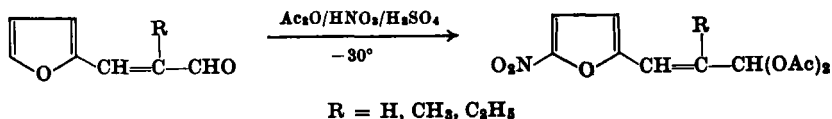
at  $-5$  to  $-30^\circ$ .<sup>94-101</sup> It is an advantage, in special cases, to use a mixture of acetyl nitrate and pyridine.

Michels and Hayes<sup>102</sup> investigated the nitration of a furan and used a mixture of acetic anhydride and nitric acid. The reaction takes place by the addition-elimination mechanism quoted above. They accomplished the nitration in the presence of weak bases, and were able to isolate a crystalline intermediate:



It is even possible to nitrate such compounds as  $\alpha,\beta$ -unsaturated furan aldehydes, ketones, carboxylic acids, etc., although in moderate yield<sup>103-105</sup>:

- <sup>94</sup> Z. N. Nazarova, *Zh. Obshch. Khim.* **24**, 575 (1954); see *Chem. Abstr.* **49**, 6214 (1955).
- <sup>95</sup> N. Saldabols, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 1, 89 (1961); see *Chem. Abstr.* **58**, 2418 (1963).
- <sup>96</sup> Z. N. Nazarova and V. N. Novikov, *Zh. Obshch. Khim.* **31**, 263 (1961); see *Chem. Abstr.* **55**, 22275 (1961).
- <sup>97</sup> R. Ueno, Japanese Patent 15,635 (1962); see *Chem. Abstr.* **59**, 9986 (1963).
- <sup>98</sup> R. Ueno, Japanese Patent 10,689 (1962); see *Chem. Abstr.* **59**, 3895 (1963).
- <sup>99</sup> H. Inoue and R. Ueno, Japanese Patent 10,688 (1962); see *Chem. Abstr.* **59**, 3895 (1963).
- <sup>100</sup> K. Venters, S. Hillers, and V. Cirule, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 1, 131 (1962); see *Chem. Abstr.* **59**, 1564 (1963).
- <sup>101</sup> J. G. Michels, G. Gever, and P. H. L. Wei, *J. Med. Pharm. Chem.* **5**, 1042 (1962); see *Chem. Abstr.* **58**, 5602 (1962).
- <sup>102</sup> J. G. Michels and K. J. Hayes, *J. Am. Chem. Soc.* **80**, 1114 (1958).
- <sup>103</sup> H. Saikachi and K. Suzuki, *Chem. Pharm. Bull. Japan* **7**, 453 and 584 (1959).
- <sup>104</sup> H. Saikachi and K. Suzuki, *Chem. Pharm. Bull. Japan* **8**, 53 (1960).
- <sup>105</sup> K. Venters and S. Hillers, *Dokl. Akad. Nauk SSSR* **137**, 83 (1961); see *Chem. Abstr.* **55**, 19907 (1961).



## 2. Halogenation

Direct halogenation of furan and its derivatives offers more difficulties. It leads to a mixture of either mono- and polysubstituted compounds or polymeric materials and resins. The reaction is usually carried out at temperatures of the order of  $-40^\circ$ , thereby hindering resinification.

a. *Chlorination*. Pozharskii<sup>106</sup> and Nazarova<sup>107</sup> carried out the reaction at higher temperatures ( $70$ – $100^\circ$ ), with the addition of inhibitors, e.g., sulfur and hydroquinone. In this way 5-chlorofurfural was obtained in 43% yield by chlorinating furfural (see also Chute and Wright<sup>108</sup>). Mastagli and Zafiriadis<sup>109</sup> obtained only the trichloro derivative of furfuryl alcohol, in 72% yield, by carrying out the chlorination at  $-30^\circ$ , in the absence of inhibitors.

b. *Bromination*. As in the case of chlorination, good results were obtained for bromination when catalytic quantities of sulfur and hydroquinone were added.<sup>94, 110</sup> Thus, furfural was converted into 5-bromofurfural in 60% yield.

*N*-Bromosuccinimide has also been used for the bromination of furan derivatives<sup>111</sup>; e.g., 2-furoic ester is converted into the 5-bromo derivative (15% yield) but furan itself resinifies.

<sup>106</sup> F. T. Pozharskii, *Uch. Zap. Rostovsk na Donu Gos. Univ.* **60**, 207 (1959); see *Chem. Abstr.* **57**, 13709 (1962).

<sup>107</sup> Z. N. Nazarova and Yu. A. Babaev, *Zh. Obshch. Khim.* **32**, 723 (1962); see *Chem. Abstr.* **58**, 5606 (1963).

<sup>108</sup> W. J. Chute and G. F. Wright, *J. Org. Chem.* **10**, 541 (1945).

<sup>109</sup> P. Mastagli and Z. Zafiriadis, *Compt. Rend.* **234**, 533 (1952).

<sup>110</sup> Z. N. Nazarova, *Dokl. Akad. Nauk Uz. SSR* No. 4, 40 (1953); see *Chem. Abstr.* **49**, 10261 (1955).

<sup>111</sup> H. Akashi, S. Hanabusa, and R. Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.* **56**, 536 (1953); see *Chem. Abstr.* **49**, 8241 (1955).

Later Terent'ev *et al.*<sup>112</sup> obtained 2-bromofuran in good yield by the action of bromine in dioxan on furan at 0°. Dioxan perbromide is now available commercially and its use for similar brominations could be advantageous.

### 3. Sulfonation

To ensure that sulfonation is successful, it seems essential that the reagent used should be free of sulfuric acid and water.<sup>113, 114</sup> If this is not the case, the reaction mixture will resinify (except in the case of furans with electron-withdrawing substituents). Pyridine-SO<sub>3</sub> complex is a suitable reagent,<sup>115</sup> and thus furan was converted into furan-2-sulfonic acid in 90% yield. The reaction was carried out in 1,2-dichloroethane at 100°. If furan is reacted with a threefold excess of pyridine-SO<sub>3</sub> reagent for 4 hours at 35–40°, furan-2,5-disulfonic acid is formed in about 80% yield.<sup>113</sup>

### 4. Acylation

a. *Formylation*. Formylation is best carried out with dimethylformamide in the presence of phosphorus oxychloride (Vilsmeier reaction) between 0 and 10°. Substitution obeys the previously mentioned rules without exception.<sup>116–119</sup> The yield for 2-formylation is between 60 and 80% but for 3-formylation only 40–50%. Thus, e.g.<sup>120</sup>,

<sup>112</sup> A. P. Terent'ev, L. I. Belen'kii, and L. A. Yanovskaya, *Zh. Obshch. Khim.* **24**, 1265 (1955); see *Chem. Abstr.* **49**, 12327 (1955).

<sup>113</sup> J. F. Scully and E. V. Brown, *J. Org. Chem.* **19**, 894 (1954).

<sup>114</sup> A. Jurasek and J. Kovac, *Sb. Prac. Chem. Fak. SVST* p. 41 (1961); see *Chem. Abstr.* **58**, 2420 (1963).

<sup>115</sup> L. A. Kazitsyna, *Uch. Zap. Moskov. Gosu. Univ.* **131**, 5 (1950); see *Chem. Abstr.* **47**, 10518 (1953).

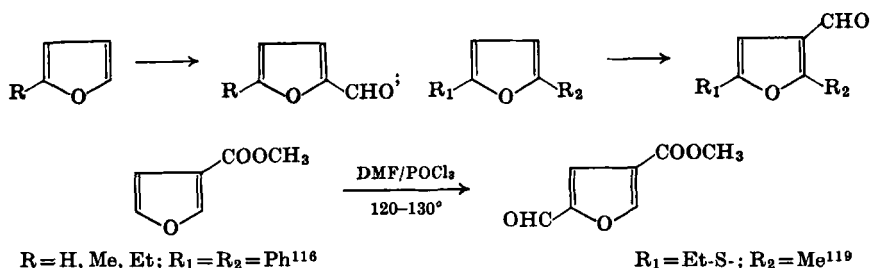
<sup>116</sup> V. J. Traynelis, J. J. Miskel, and J. R. Sowa, *J. Org. Chem.* **22**, 1269 (1957).

<sup>117</sup> D. A. H. Taylor, *J. Chem. Soc. (London)* p. 2767 (1959).

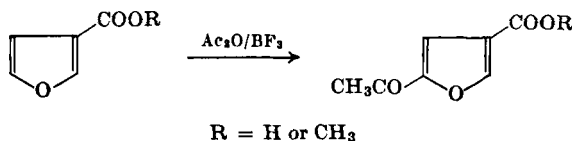
<sup>118</sup> A. L. Mndzhoyan, V. G. Afrikyan, M. T. Grigoryan, and E. A. Markaryan, *Dokl. Akad. Nauk. Arm. SSR* **27**, 301 (1960); see *Chem. Abstr.* **54**, 481 (1960).

<sup>119</sup> Ya. L. Gol'dfarb, Ya. L. Danyushevskii, and M. A. Vinogradova, *Dokl. Akad. Nauk SSSR* **151**, 332 (1963); see *Chem. Abstr.* **59**, 8681 (1963).

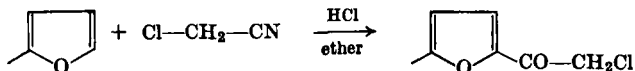
<sup>120</sup> G. Zwicky, P. G. Waser, and C. H. Eugster, *Helv. Chim. Acta* **42**, 1177 (1959).



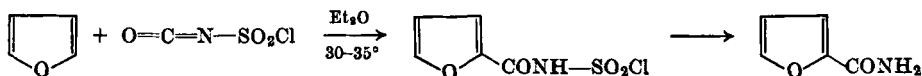
b. *Other Acylations.* These reactions are best effected with Lewis acid catalysts as  $\text{SnCl}_4$ ,<sup>69</sup>  $\text{ZnCl}_2$ ,<sup>121</sup>  $\text{BF}_3$ -etherate,<sup>122, 123</sup>  $\text{H}_3\text{PO}_4$ .<sup>28, 119</sup> Yields are very variable. The substitution rules are obeyed here also, e.g.<sup>124</sup>



Taylor has carried out a successful Hoesch reaction with silvan<sup>117</sup>:



The reaction between furan and *N*-carbonylsulfamoyl chloride yields derivatives of 2-furoic acid<sup>125</sup>:



### 5. Alkylation

The alkylation of furans containing electron-withdrawing groups is possible with Friedel-Crafts catalysts. 2-Acetylfuran yields 2-acetyl-

<sup>121</sup> S. Hillers and I. Berklaiva, *Latvijas PSR Zinatnu Akad. Vestis* No. 4 p. 53 (1956); see *Chem. Abstr.* **51**, 5747 (1957).

<sup>122</sup> P. A. Finan and G. A. Fothergill, *J. Chem. Soc.* p. 2262 (1962).

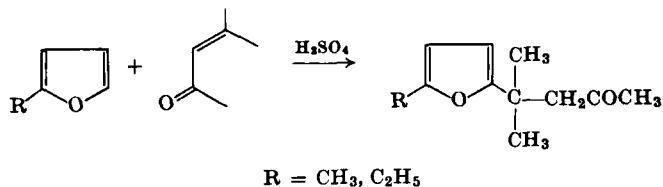
<sup>123</sup> P. A. Finan and G. A. Fothergill, *J. Chem. Soc.* p. 2723 (1963).

<sup>124</sup> C. H. Eugster and P. G. Waser, *Helv. Chim. Acta* **40**, 888 (1957).

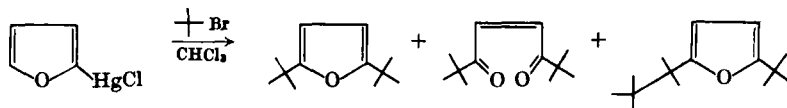
<sup>125</sup> R. Graf, *Ann.* **661**, 111 (1963).

4-isopropylfuran, in 15% yield.<sup>126</sup> An alternative catalyst is ferric chloride, which can be used in the benzylation of 2-carbomethoxyfuran.<sup>127</sup>

A new investigation of the Friedel-Crafts alkylation of 2-furoic esters with *sec*-butyl bromide (using  $\text{AlCl}_3$  in  $\text{CS}_2$ ) yielded a mixture of 43% 5-*tert*-butyl-2-furoic ester and 57% 5-*sec*-butyl-2-furoic ester.<sup>128</sup> However, examples are known where, under other conditions, even furans which are not negatively substituted can be successfully alkylated. In this way 2-methyl- and 2-ethylfuran condense with mesityl oxide in the presence of strong sulfuric acid<sup>129,130</sup> (see also similar reactions mentioned in Sections III, B, III, C, and IV, B, 3):



The chloromeric derivative of furan is also suitable for alkylation. When *tert*-butyl bromide is added to the solution of this compound in chloroform, an exothermic reaction takes place. Three products were isolated from the reaction mixture, with 2,5-di-*tert*-butylfuran in moderate yield<sup>131</sup>:



A mono-*tert*-butylfuran can be isolated in small yield using isobutylene with  $\text{BF}_3$  catalyst.<sup>131</sup>

<sup>126</sup> N. Elming, *Acta Chem. Scand.* **6**, 605 (1952).

<sup>127</sup> I. P. Tsukervanik and G. G. Galust'yan, *Dokl. Akad. Nauk Uz. SSR* **20**, 26 (1963); see *Chem. Abstr.* **59**, 6341 (1963).

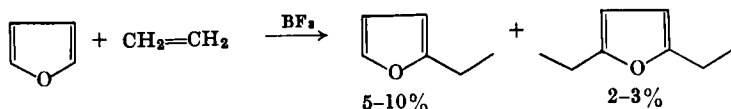
<sup>128</sup> C. D. Hurd and G. L. Oliver, *J. Am. Chem. Soc.* **76**, 50 (1954).

<sup>129</sup> Yu. K. Yur'ev, N. S. Zefirov, A. A. Štejnman, and V. M. Gurevič, *Zh. Obshch. Khim.* **30**, 411 (1960); see *Chem. Abstr.* **54**, 24628 (1960).

<sup>130</sup> V. G. Glukhovtsev, S. V. Zakharova, and A. D. Petrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 906 (1963); *Dokl. Akad. Nauk SSSR* **151**, 570 (1963); see *Chem. Abstr.* **59**, 7454 and 12738 (1963).

<sup>131</sup> W. H. Brown and G. F. Wright, *Can. J. Chem.* **35**, 236 (1957).

Other alkylations of furans with olefins, catalyzed by  $\text{BF}_3$ -etherate, are known.<sup>132-136</sup> The yield is often poor and the reactions lead to a mixture of mono and bis adducts,<sup>137</sup> e.g.,



(It is known that ethylene under pressure can give a normal diene adduct also.)

Isomerizations can also take place (e.g., with propylene, a mixture of *n*-propyl- and isopropylfurans forms), and it has been shown that the 3-position reacts in certain cases.<sup>134</sup> The addition to  $\alpha,\beta$ -unsaturated carbonyl compounds goes somewhat more easily, and this will be described later.

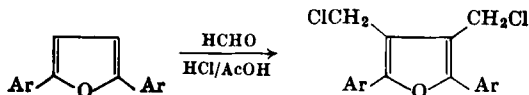
#### 6. Chloromethylation and Other Condensation Reactions with Carbonyl Compounds

These reactions result in 2 or 3 substitution, but 2 substitution is preferred. Generally the yield varies between 80 and 90%.<sup>138-142</sup>

- <sup>132</sup> H. Pines and J. A. Vesely, U.S. Patent 2,532,515 (1950); see *Chem. Abstr.* **45**, 2982 (1951).
- <sup>133</sup> A. Harban and C. E. Johnson, U.S. Patent 2,641,600 (1953); see *Chem. Abstr.* **48**, 5224 (1954).
- <sup>134</sup> S. Hillers and A. Berzins, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 1, 103 (1962); see *Chem. Abstr.* **59**, 1564 (1963).
- <sup>135</sup> S. Hillers and A. Berzins, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 1, 113 (1962); see *Chem. Abstr.* **59**, 1564 (1963).
- <sup>136</sup> S. Hillers and A. Berzins, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 3, 445 (1962); see *Chem. Abstr.* **59**, 5106 (1963).
- <sup>137</sup> S. Hillers, A. Berzins, and L. Lauberte, *Latvijas PSR Zinatnu Akad. Vestis, Kim. Ser.* No. 4, 71 (1958); see *Chem. Abstr.* **53**, 325 (1959).
- <sup>138</sup> R. Andrisano, *Ann. Chim. (Rome)* **40**, 30 (1950); see *Chem. Abstr.* **45**, 7563 (1951).
- <sup>139</sup> A. Tundo, *Boll. Sci. Fac. Chim. Ind. Bologna* **14**, 63 (1956); see *Chem. Abstr.* **51**, 5748 (1957).
- <sup>140</sup> Y. Hachihama, T. Shono, and K. Hyono, *Technol. Rept. Osaka Univ.* **8**, 475 (1958); see *Chem. Abstr.* **53**, 18933 (1959).
- <sup>141</sup> A. L. Mndzhoyan and A. A. Aroyan, *Dokl. Akad. Nauk. Arm. SSR* **27**, 101 (1958); see *Chem. Abstr.* **53**, 18934 (1959).
- <sup>142</sup> R. Lukeš, M. Janda, and M. Valenta, Czech. Patent 94,213 (1960); see *Chem. Abstr.* **55**, 4531 (1961).

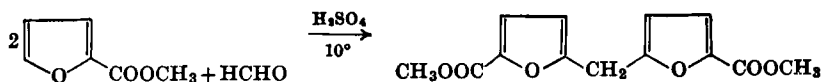
Only furans with electron-withdrawing substituents can be successfully reacted; e.g., Mndzhoyan<sup>143</sup> converted 5-methyl-2-carbomethoxyfuran to the 4-chloromethyl compound.

2-Carbomethoxyfuran can be chloroethylated in 77% yield.<sup>144</sup> 2,5-Diphenylfuran can be bischloromethylated<sup>145</sup>:

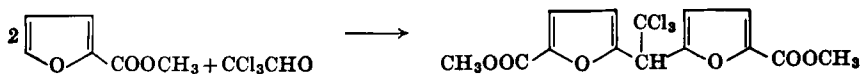


2-Chloromethylfuran gave the 2,5-bischloromethyl compound.<sup>146</sup>

In the presence of  $\text{H}_2\text{SO}_4$ , two moles of 2-carbomethoxyfuran react with one mole of formaldehyde to form bis-(5-carbomethoxy-2-furyl)methane<sup>147</sup>:



With chloral the analogous compound forms<sup>148</sup>:



Furan and its homologs react in the same way. These compounds were of interest because of their similarity to DDT. They can easily be converted into difurylalkanes, which are otherwise usually difficult

<sup>143</sup> A. L. Mndzhoyan, V. G. Afrikyan, M. T. Grigoryan, and E. A. Markaryan, *Dokl. Akad. Nauk Arm. SSR* **25**, 277 (1957); see *Chem. Abstr.* **52**, 12835 (1958).

<sup>144</sup> A. L. Mndzhoyan and A. A. Aroyan, *Dokl. Akad. Nauk Arm. SSR* **25**, 267 (1957); see *Chem. Abstr.* **52**, 12834 (1958).

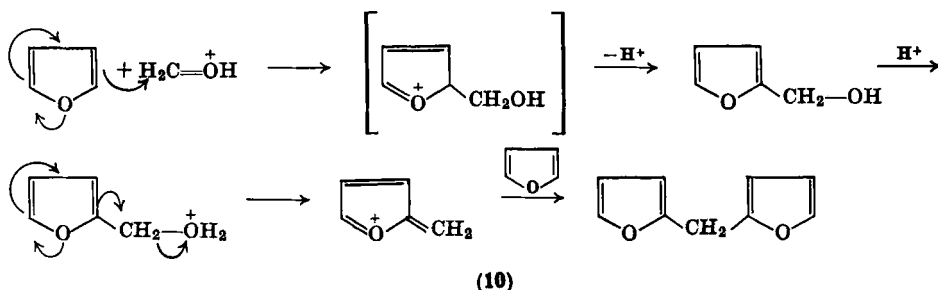
<sup>145</sup> S. Adjangba, D. Billet, and C. Mentzer, *Bull. Soc. Chim. France* p. 132 (1962).

<sup>146</sup> K. Yu. Novitskii, V. P. Volkov, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **32**, 538 (1961); see *Chem. Abstr.* **55**, 23485 (1961).

<sup>147</sup> L. Decsei, B. Zsádon, and G. Reichmann, *Magy. Kem. Folyoirat* **69**, 328 (1963); see *Chem. Abstr.* **59**, 11394 (1963).

<sup>148</sup> J. R. Willard and C. S. Hamilton, *J. Am. Chem. Soc.* **73**, 4805 (1951).

to obtain. Sawatzky and Brown<sup>149</sup> found that furan itself, on reaction with formaldehyde, gave a yield of only 1.7%:



Cation 10 can electrophilically attack a further molecule of furan, finally yielding difurylmethane.

Acetaldehyde, levulinic acid, and pyruvic acid also react with furan and 2-methylfuran. Acetoacetic ester reacts, but does not give rise to definite products. Alkylvinyl ethers can be reacted as aldehydes.<sup>150</sup>

Furan reacts with dimethyl and diethyl ketone in the presence of hydrochloric acid, via various intermediate steps, to give the anhydro-tetramers, the so-called quaterenes (11)<sup>151-153</sup>:

### 7. The Mannich Reaction

This reaction can be carried out only with alkyl-substituted furans. The following is a recent example<sup>154</sup>:



The yield is 70%. Other examples are described.<sup>155-157</sup>

<sup>149</sup> W. H. Brown and H. Sawatzky, *Can. J. Chem.* **34**, 1147 (1956).

<sup>150</sup> M. F. Shostakovskii, A. V. Bogdanova, and A. N. Volkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 2224 (1962); see *Chem. Abstr.* **58**, 13881 (1963).

<sup>151</sup> R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.* **20**, 1147 (1955).

<sup>152</sup> R. E. Beals and W. H. Brown, *J. Org. Chem.* **21**, 447 (1956).

<sup>153</sup> W. H. Brown and W. N. French, *Can. J. Chem.* **36**, 537 (1958).

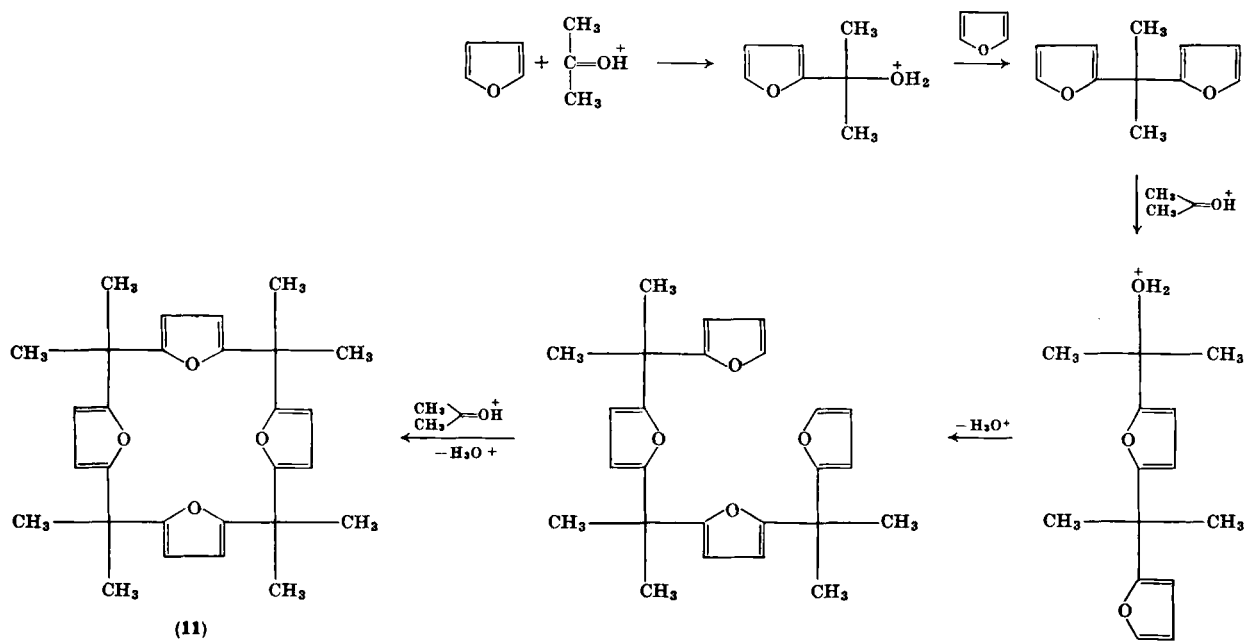
<sup>154</sup> E. W. Gill and H. R. Ing, *J. Chem. Soc.* p. 4728 (1958).

<sup>155</sup> R. F. Holdren and R. M. Hixon, *J. Am. Chem. Soc.* **68**, 1198 (1946).

<sup>156</sup> E. L. Eliel and P. E. Peckham, *J. Am. Chem. Soc.* **72**, 1209 (1950).

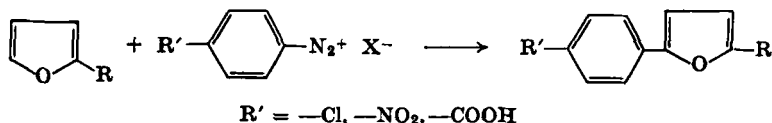
<sup>157</sup> H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.* **82**, 1428 (1960).



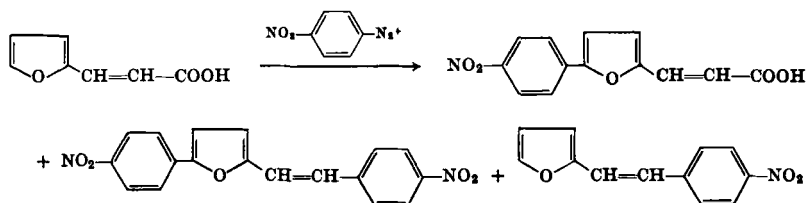


### 8. Arylation

The furan ring undergoes arylation with diazo compounds, but the yield is poor. Thus, furfural,<sup>23</sup> 2-furoic acid,<sup>158</sup> and furylacrylic acid can be converted into 5-substituted arylfuran derivatives by diazonium salts (see further references in Ref. 159):



The reaction is best carried out using the Meerwein reaction conditions (acetone-water/ $\text{CuCl}_2$ ). Analogous reactions were described for diazoarsanilic acid and furan.<sup>160</sup> The course of the reaction with 2-furylacrylic acid is more complex, as decarboxylation occurs and diarylated compounds form<sup>161</sup>:



Phenylsulfenyl chloride also substitutes 2-furoic ester in the 5-position, in the presence of a peroxide, to give 5-phenylthio-2-furoic ester, in 5% yield.<sup>162</sup>

### B. ADDITIONS OF $\alpha,\beta$ -UNSATURATED ALDEHYDES, KETONES, AND NITRO COMPOUNDS TO FURANS

It is well known that simple furans, e.g., furan and 2-methylfuran, do not react with  $\alpha,\beta$ -unsaturated aldehydes and ketones under Diels-Alder reaction conditions.<sup>163</sup> If the reaction is catalyzed by

<sup>158</sup> K. B. L. Mathur and H. S. Mehra, *J. Chem. Soc.* p. 2576 (1961).

<sup>159</sup> C. S. Rondestvedt, *Org. Reactions* **11**, 201 (1960).

<sup>160</sup> W. Freund, *J. Chem. Soc.* p. 3073 (1952).

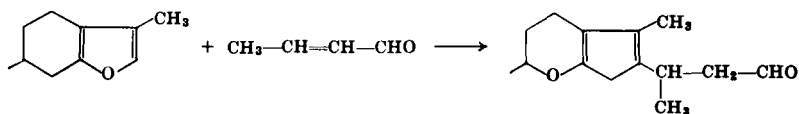
<sup>161</sup> W. Freund, *J. Chem. Soc.* p. 3068 (1952).

<sup>162</sup> H. Akashi, S. Hanabusa, and R. Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.* **56**, 718 (1953); see *Chem. Abstr.* **49**, 7545 (1955).

<sup>163</sup> H. H. Holmes, *Org. Reactions* **4**, 87 (1948).

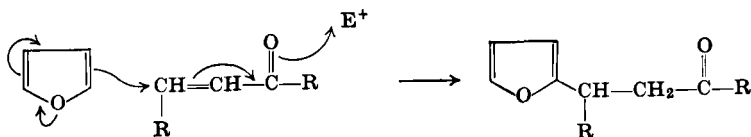
SO<sub>2</sub>, addition and substitution occurs. This type of reaction is familiar from pyrrole chemistry. It is possible to prepare derivatives of 2-furylpropionaldehyde by its application.

Furan itself is most likely to undergo reaction in the 2-positions, e.g., with nitroethylene,<sup>164</sup> acrolein,<sup>130, 165-168</sup> and other  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>130, 169</sup> Yur'ev and co-workers<sup>166</sup> suggest that 4,5,6,7-tetrahydro-3,6-dimethylbenzofuran (menthofuran) reacts with crotonaldehyde as follows:



Sulfur dioxide is the most usual catalyst in these reactions.

No evidence is yet available to show that the mechanism of these reactions is analogous to the accepted acid-catalyzed substitution by olefins:



SO<sub>2</sub> seems to be a very specific catalyst. It is not excluded that the reaction goes via the same orientated complex which results in a Diels-Alder adduct under normal conditions. In this connection, it should be noted that the normal addition of acrylic ester and acrylonitrile to 3,4-dimethoxyfuran, according to Eugster and Hofmann,<sup>170</sup> proceeds *without* added acid.

<sup>164</sup> Yu. K. Yur'ev, N. S. Zefirov, and R. A. Ivanova, *Zh. Obshch. Khim.* **33**, 3512 (1963); see *Chem. Abstr.* **60**, 7971 (1964).

<sup>165</sup> I. D. Webb and G. T. Borchardt, U.S. Patent 2,640,057 (1953); see *Chem. Abstr.* **48**, 4595 (1954).

<sup>166</sup> Yu. K. Yur'ev, N. S. Zefirov, and A. A. Shteinman, *Zh. Obshch. Khim.* **33**, 1150 (1963); see *Chem. Abstr.* **59**, 11395 (1963).

<sup>167</sup> Yu. K. Yur'ev, N. S. Zefirov, and R. A. Ivanova, *Zh. Obshch. Khim.* **33**, 3512 (1963).

<sup>168</sup> A. A. Ponomarev and I. A. Markushina, *Zh. Obshch. Khim.* **33**, 3955 (1963); see *Chem. Abstr.* **60**, 10649 (1964).

<sup>169</sup> E. Buchta and F. Fuchs, *Ann.* **655**, 81 (1962).

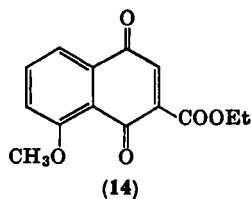
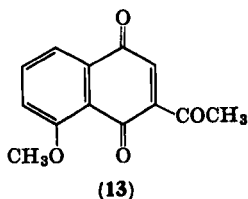
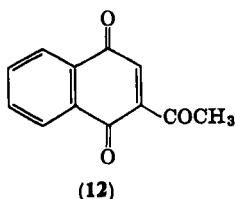
<sup>170</sup> C. H. Eugster and A. Hofmann, *Chimia (Aarau)* **15**, 518 (1961).

### C. ADDITION OF NEGATIVELY SUBSTITUTED QUINONES TO FURANS

Recently Eugster and co-workers have observed that furans react with various negatively substituted quinones by substitution and addition.<sup>171-177</sup> These reactions have different rates, and may go without the addition of a catalyst. However, this does not mean that they are not to be treated analogously to the acid-catalyzed reactions.

The following reactions were carried out:

The following naphthoquinones react in an analogous way:



The results can be summarized as follows.

The most rapid reaction occurs with dimethoxyfuran; its reaction with acetylbenzoquinone is strongly exothermic. Depending on the reaction conditions, varying amounts of mono or di adducts form as their hydroquinones. The furylquinones themselves are easily prepared by  $\text{MnO}_2$  oxidation. The mono adduct can be converted into the di adduct by reaction with acetylbenzoquinone. In the naphthaquinone series the reactions are somewhat slower. Mostly mixtures of quinones and hydroquinones form, with the latter predominating.

Furan, 2-methylfuran, and other compounds react slowly in the naphtho series. The quinones form as a result of oxido-reduction. The yields are moderate with acetylnaphthaquinone (12), but with the methoxylated quinones (13) and (14) there is no reaction in a

<sup>171</sup> C. H. Eugster and P. Bosshard, *Chimia (Aarau)* **15**, 528 and 530 (1961).

<sup>172</sup> C. H. Eugster and P. Bosshard, *Chimia (Aarau)* **16**, 45 (1962).

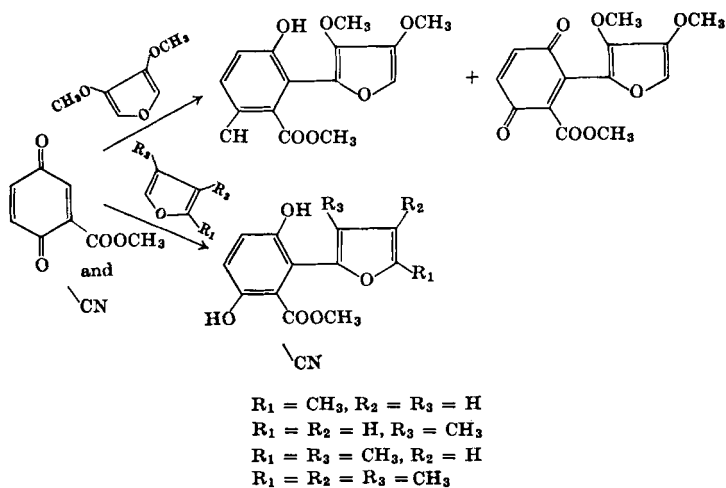
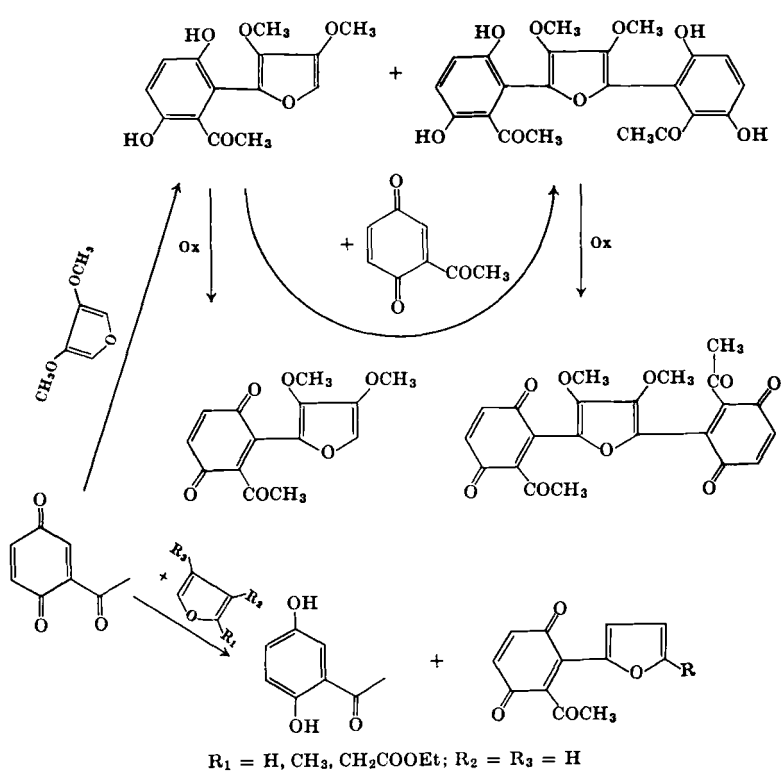
<sup>173</sup> C. H. Eugster and R. Good, *Chimia (Aarau)* **16**, 343 (1962).

<sup>174</sup> C. H. Eugster and P. Bosshard, *Helv. Chim. Acta* **46**, 815 (1963).

<sup>175</sup> C. H. Eugster and P. Bosshard, *Angew. Chem.* **75**, 101 (1963).

<sup>176</sup> P. Bosshard, S. Fumagalli, R. Good, W. Trueb, W. von Philipsborn, and C. H. Eugster, *Helv. Chim. Acta* **47**, 769 (1964).

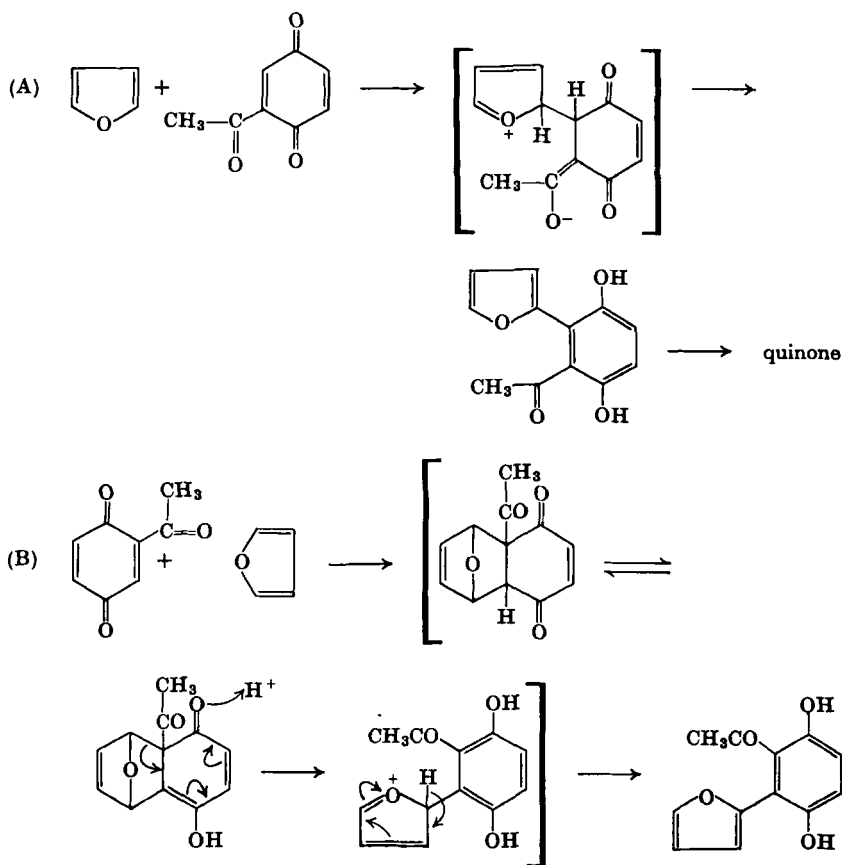
<sup>177</sup> C. H. Eugster and N. Baumann, Unpublished work (1965).



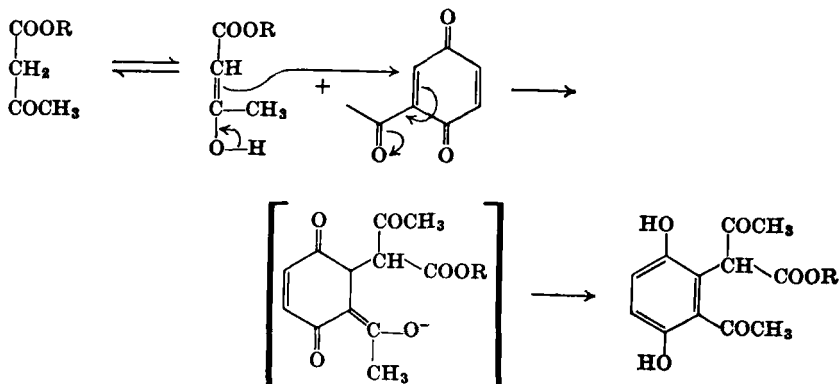
sealed tube. A small yield is obtained when anhydrous zinc chloride is added.

All products crystallize well. They were the first furylquinones known. These compounds are potentially of synthetic use, and their reactions will be described in Section VII. They have unusual UV and IR spectra.<sup>174, 176</sup>

There are essentially two mechanisms to be considered for these orthofurylation reactions. First, a direct nucleophilic addition of furan, to the acylquinone at the 2-position is postulated, which is probably catalyzed by traces of acid (route A). The other leads through a Diels-Alder addition, and the adduct yields a stable hydroquinone by a dienone-phenol rearrangement (route B).



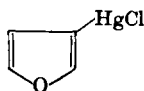
Recent work<sup>176</sup> shows that route A is more probable. Acetoacetic ester, vinyl ethers, and enamines react analogously with acetylbenzoquinone. The reaction of acetoacetic ester probably goes via the enol form, as the reaction rate is solvent-dependent, i.e., it depends on the enol content<sup>176</sup>:



In all these reactions the first stable product to form must be hydroquinone. In those cases where quinones are the end product, there is an oxidation-reduction, where the hydroquinone initially formed is oxidized by the acetylbenzoquinone present. This is true for slow additions only. The reaction between 3,4-dimethoxyfuran and acetylbenzoquinone does not proceed further than the hydroquinone stage. This is due not only to the somewhat enhanced reaction rate, but also to the poor solubility of the products, and to the stabilization of the hydroquinone by strong hydrogen bonding to the basic furan ring.

#### D. METALATION OF THE FURAN RING

Metal derivatives of furans of type **15** are found to be valuable intermediates in the preparation of 3-substituted furans which are otherwise not readily accessible. **15** can be obtained from 2-furoic acid.



(15)

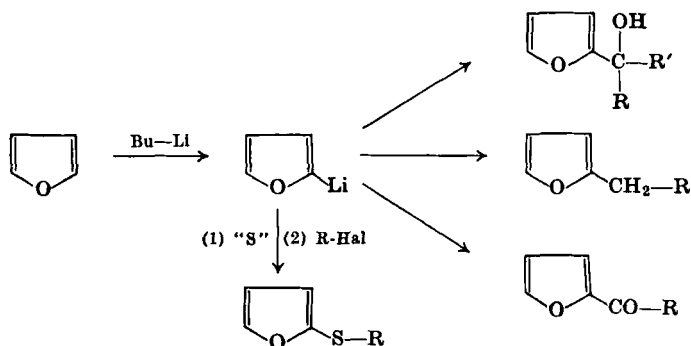
Reaction of the acid with mercuric acetate in water yields the mercury salt. This is transformed to the desired product (**15**) by pyrolysis and finally by mixing with 95% acetic acid.<sup>178</sup> The 2-substituted mercury salt is also formed, but only in 5% yield.

Verkade and co-workers<sup>179</sup> described a somewhat different method of mercuration of the furan ring. They converted furan into **15** by direct reaction with  $\text{HgCl}_2$  in water, in the presence of sodium acetate and ethanol.

When **15** is reacted with  $\text{KI/I}_2$  and water, 3-iodofuran forms,<sup>178</sup> which is converted into 3-methoxyfuran, 3-cyanofuran, and 3-furyl methyl sulfide by various nucleophiles.<sup>180</sup>

With butyl lithium at  $-70^\circ$ , 3-iodofuran is converted into the lithium compound, which with dimethylformamide or carbon dioxide gives 3-formylfuran or 3-furoic acid, respectively.<sup>180</sup>

The introduction of lithium into the 2-position of the furan ring, which was studied earlier by Gilman and co-workers, has recently been improved:



Condensation of 2-lithiofuran with aldehydes, ketones, and esters<sup>181</sup> is more effective than the carboxylation reaction which has been

<sup>178</sup> S. Gronowitz and G. Sörlin, *Arkiv Kemi* **19**, 515 (1962); see *Chem. Abstr.* **58**, 5606 (1963).

<sup>179</sup> P. E. Verkade, T. Morel, and H. G. Gerritsen, *Rec. Trav. Chim.* **74**, 763 (1955).

<sup>180</sup> S. Gronowitz and G. Sörlin, *Acta Chem. Scand.* **15**, 1419 (1961).

<sup>181</sup> V. Ramanathan and R. Levine, *J. Org. Chem.* **27**, 1216 (1962).



known for a long time. Alkylation with halides gives variable yields.<sup>181, 182</sup> Ketones can be obtained from nitriles. Conversion into the sulfinic acid can be effected with SO<sub>2</sub>, which can in turn be oxidized to the sulfonic acid.<sup>113</sup> The 2-thioether can be obtained by reaction with sulfur and an alkyl halide.<sup>119</sup> 2-Alkylation has been carried out with sodium and alkyl halides as well.<sup>183</sup>

#### IV. Addition Reactions at the Furan Ring

The addition reaction to the furan ring which has been by far the most studied is certainly the catalytic hydrogenation of the ring. It has been shown in the numerous publications on this reaction that various classes of compounds can be obtained—alcohols, ketones, hydrocarbons, ethers, and others. The extent of the literature on this subject severely limits an exhaustive treatment, which is not possible within the framework of this chapter. We are able to mention only a small part of the work. A complete review, with particular reference to recent Russian work, has been given by Bel'skii and Shuikin.<sup>184</sup>

##### A. HYDROGENATION

The catalytic hydrogenation of furan and its derivatives is strongly dependent on reaction conditions and catalysts employed. A review is available.<sup>185</sup> It is possible to classify the results of these reactions into three main groups:

- (1) hydrogenation of the furan ring without hydrogenolysis;
- (2) hydrogenolysis of the furan ring;
- (3) hydrogenation of the unsaturated side chains:
  - (a) with simultaneous hydrogenation of the furan ring,
  - (b) without hydrogenation of the furan ring.

<sup>182</sup> F. Bohlmann, H. Jastrow, G. Ertingshausen, and D. Kramer, *Ber.* **97**, 801 (1964).

<sup>183</sup> Office de Recherches Industrielles de Laboratoire, French Patent 1,186,346 (1959); see *Chem. Abstr.* **56**, 455 (1962).

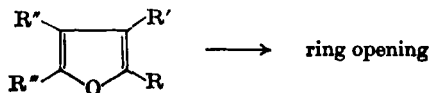
<sup>184</sup> I. F. Bel'skii and N. I. Shuikin, *Russ. Chem. Rev. (Engl. Transl.)* **32**, 307 (1963).

<sup>185</sup> N. I. Shuikin and I. F. Bel'skii, *Actes 2e Congr. Intern. Catalyse, Paris, 1960* Vol. 2, p. 2625. Editions Technip, Paris, 1961; see *Chem. Abstr.* **55**, 27258 (1961).

(1) A great deal of work has been reported on the conversion of furan into tetrahydrofuran derivatives.<sup>185, 143, 157, 174, 186-197</sup> A nickel catalyst is usually used, and the reaction is carried out in the vapor phase at temperatures between 80 and 160° and at pressures of up to 160 atmospheres. No detailed work has been done on the stereochemistry of the products obtained.

Tetrahydrofuran-2,3,4,5-*d*<sub>4</sub> was obtained by Bissell and Finger<sup>198</sup> by deuteration of furan under pressure using Rh/Al<sub>2</sub>O<sub>3</sub>/D<sub>2</sub>.

(2) Reductions with hydrogenolysis of the furan ring:



This reaction is carried out similarly in the gas phase,<sup>193, 199-206</sup> but

<sup>186</sup> S. Swadesh, S. Smith, and A. P. Dunlop, *J. Org. Chem.* **16**, 476 (1951).

<sup>187</sup> Z. Zafiriadis and P. Mastagli, *Compt. Rend.* **232**, 519 (1951).

<sup>188</sup> Quaker Oats Co., British Patent 780,275 (1957); see *Chem. Abstr.* **52**, 20196 (1958).

<sup>189</sup> A. S. Sultanov, *Vopr. Ispol'z. Pentozansoderzh. Syr'ya, Tr. Vses. Soveshch. Riga, 1955* p. 277 (1958); see *Chem. Abstr.* **53**, 14077 (1959).

<sup>190</sup> J. Wang, Chih-Kuang Yen, and Shih-Tsin Li, *K'o Hsüeh T'ung Pao* p. 434 (1958); see *Chem. Abstr.* **53**, 11333 (1959).

<sup>191</sup> N. I. Shuikin and I. F. Bel'skii, *Zh. Obshch. Khim.* **29**, 1093 (1959); see *Chem. Abstr.* **54**, 1481 (1960).

<sup>192</sup> N. I. Shuikin, I. F. Bel'skii, and O. N. Savekina, *Zh. Obshch. Khim.* **29**, 869 (1959); see *Chem. Abstr.* **54**, 1482 (1960).

<sup>193</sup> S. Mitsui, Y. Ishikawa, and Y. Takeuchi, *Nippon Kagaku Zasshi* **81**, 286 (1960); see *Chem. Abstr.* **56**, 436 (1962).

<sup>194</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **131**, 1117 (1960); see *Chem. Abstr.* **54**, 21033 (1960).

<sup>195</sup> Sterling Drug Inc., British Patent 907,528 (1962); see *Chem. Abstr.* **58**, 6802 (1963).

<sup>196</sup> D. G. Manly (Quaker Oats Co.), U.S. Patent 3,021,342 (1962); see *Chem. Abstr.* **56**, 15489 (1962).

<sup>197</sup> A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, *Zh. Obshch. Khim.* **33**, 1778 (1963); see *Chem. Abstr.* **59**, 11396 (1963); see also numerous earlier investigations on the reduction of furans.

<sup>198</sup> E. R. Bissell and M. Finger, *J. Org. Chem.* **24**, 1259 (1959).

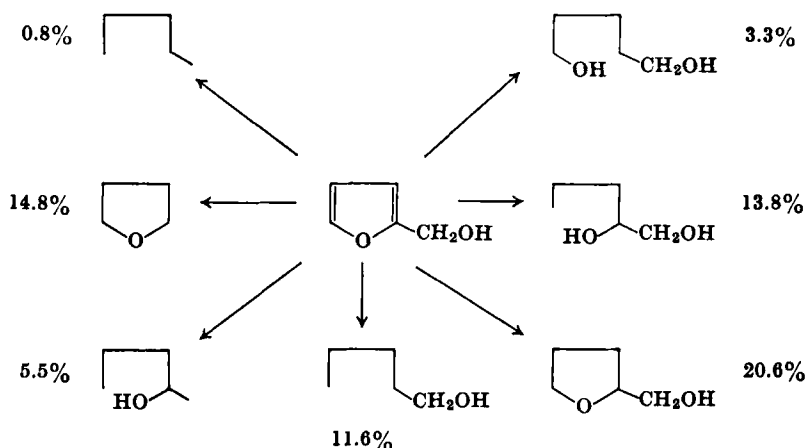
<sup>199</sup> N. I. Shuikin, I. F. Bel'skii, and Sin-Khua Tyan, *Dokl. Akad. Nauk SSSR* **116**, 808 (1957); see *Chem. Abstr.* **52**, 6305 (1958).

<sup>200</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **115**, 330 (1957); see *Chem. Abstr.* **52**, 6305 (1958).

<sup>201</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **116**, 621 (1957); see *Chem. Abstr.* **52**, 5368 (1958).

usually at higher temperatures than the reactions described in (1). The reaction, however, is appreciably more complex, as a single product seldom forms. The course of the reaction and the kind of products obtained cannot be foretold with certainty. Several of the metals of group VII of the periodic system can be used as catalysts, on a variety of carriers.

The variety of reaction products can be demonstrated by the following examples. Alcohols usually form with platinum oxide catalysts; e.g., in the case of furfuryl alcohol with Adams catalyst in ethanol, at least seven reaction products are obtained:



However, the same author obtained tetrahydrofurfuryl alcohol in nearly quantitative yield, with a rhodium-platinum oxide catalyst in ethanol, and also in glacial acetic acid, i.e., without hydrogenolysis.<sup>207</sup> Nickel skeleton catalysts also yield mainly alcohols as hydrogenolysis products at 175° in a continuous system:

<sup>202</sup> N. I. Shuikin, I. F. Bel'skii, and R. A. Karakhanov, *Dokl. Akad. Nauk SSSR* **122**, 625 (1958); see *Chem. Abstr.* **53**, 4247 (1959).

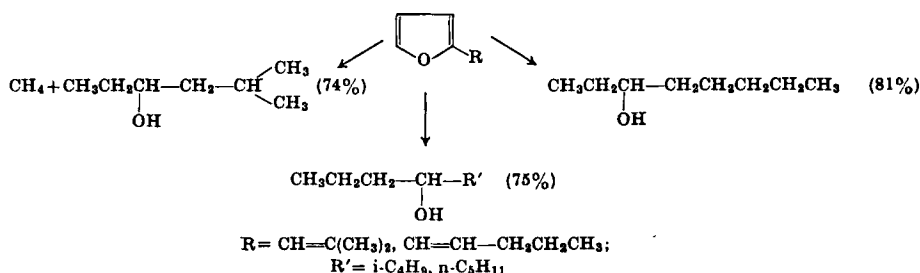
<sup>203</sup> N. I. Shuikin, and I. F. Bel'skii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 309 (1958); see *Chem. Abstr.* **52**, 12834 (1958).

<sup>204</sup> N. I. Shuikin, I. F. Bel'skii, and G. K. Vasilevskaya, *Z. Chem.* **2**, 359 (1962); see *Chem. Abstr.* **59**, 2750 (1963).

<sup>205</sup> N. I. Shuikin, I. F. Bel'skii, and G. K. Vasilevskaya, *Zh. Obshch. Khim.* **32**, 2911 (1962); see *Chem. Abstr.* **58**, 9006 (1963).

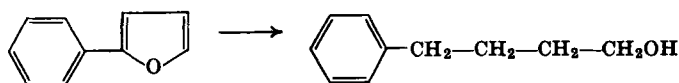
<sup>206</sup> K. Thewalt and W. Rudolph, *Ber.* **96**, 136 (1963).

<sup>207</sup> S. Nishimura, *Bull. Chem. Soc. Japan* **34**, 32 (1961).



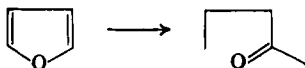
The corresponding ketones are also formed.<sup>208</sup>

The reduction of 2-phenylfuran to 4-phenylbutanol in glacial acetic acid with Pd/charcoal is very specific, in that the yield is nearly 80%<sup>193</sup>:



On the other hand, Raney nickel in ethanol gives only 32% of 4-phenylbutanol, and yields at least five by-products. Ketones are the main or subsidiary products in many hydrogenolyses.<sup>208</sup>

Hydrogenation of 2-methylfuran over a metallic Cu-Al catalyst under normal pressure yields methyl *n*-propyl ketone:



At higher pressure the furan ring opens at either of the C—O bonds, and the carbonyl group formed is simultaneously reduced to the alcohol. If the temperature is raised, dehydrogenation of the alcohols previously formed to ketones occurs and even larger yields of hydrocarbons are formed.<sup>209</sup> The products obtained with Pd-Al skeleton catalysts at 250–275°, <sup>210</sup> and with Ni-CdO catalysts at 300°, <sup>211</sup> are

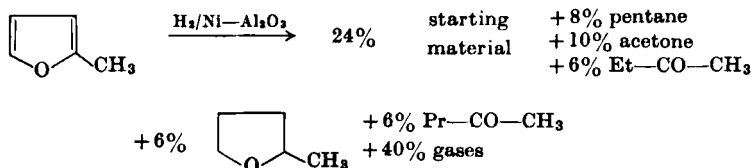
<sup>208</sup> N. I. Shuikin and I. F. Bel'skii, *Zh. Obshch. Khim.* **27**, 402 (1957); see *Chem. Abstr.* **51**, 15489 (1957).

<sup>209</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **131**, 109 (1960); see *Chem. Abstr.* **54**, 12092 (1960).

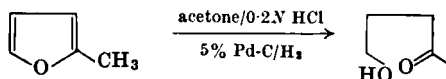
<sup>210</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **125**, 345 (1959); see *Chem. Abstr.* **53**, 20015 (1959).

<sup>211</sup> N. I. Shuikin and I. F. Bel'skii, *Zh. Obshch. Khim.* **29**, 3627 (1959); see *Chem. Abstr.* **54**, 19634 (1960).

entirely analogous, while with  $\text{Ni-Al}_2\text{O}_3$  at  $400^\circ$  the following results were obtained<sup>200</sup>:



In favorable cases aliphatic ketones can be prepared in 92–95% yields from alkylfurans,<sup>201</sup> e.g., in the following way<sup>212</sup>:



On the other hand, Gavrilova and Gonikberg opened the furan ring with hydrogen, without the use of catalysts.<sup>213</sup> The reaction is carried out at high temperature ( $350\text{--}375^\circ$ ) and at a pressure between 240 and 750 atmospheres, in the absence of a solvent. The following products are obtained from 2-methylfuran: acetone, methyl ethyl ketone, methyl butyl ketone, methyl amyl ketone, acetophenone, methylpropylcarbinol, *n*-pentane, and water. The authors suggest that these products are formed by a free radical mechanism.

(3a) Furan derivatives with unsaturated side chains can easily be reduced to saturated tetrahydrofuran derivatives.<sup>193, 214–217</sup> Thus, 2-furylacrylic acid gives tetrahydrofurylpropionic acid with Raney nickel at normal temperature and pressure,<sup>193</sup> while furfural with copper chromite, at  $150\text{--}200^\circ$  and 250 atmospheres, gives tetrahydrofurfuryl alcohol.<sup>216</sup>

<sup>212</sup> T. E. Londergan, N. L. Hause, and W. R. Schmitz, *J. Am. Chem. Soc.* **75**, 4456 (1953).

<sup>213</sup> A. E. Gavrilova and M. G. Gonikberg, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **344** (1960); see *Chem. Abstr.* **54**, 21034 (1960).

<sup>214</sup> M. Yokoyama and R. Hasuo, *Kôgakuin Daigaku Konkyû Hôkoku* **1**, 76 (1954); see *Chem. Abstr.* **53**, 14093 (1959).

<sup>215</sup> Sterling Drug Inc., British Patent 907,528 (1962); see *Chem. Abstr.* **58**, 6802 (1963).

<sup>216</sup> E. Haidegger, L. Hodossy, and I. Peter, Hungarian Patent 147,519 (1960); see *Chem. Abstr.* **58**, 9027 (1963).

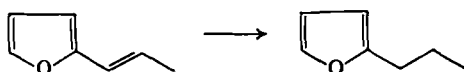
<sup>217</sup> N. I. Shuikin, A. D. Petrov, V. G. Glukhovtsev, and R. A. Karakhanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 521 (1963); see *Chem. Abstr.* **59**, 2749 (1963).

(3b) A more difficult problem is encountered when it is necessary to reduce selectively multiple bonds in the side chain, especially when they are conjugated with the nucleus. Up to the present time little has been published on this subject. The best method for the side chain reduction of  $\beta$ -2-furylacrylic acid seems to be with Raney alloy in dilute NaOH.<sup>117</sup> If the reaction is carried out more drastically, the nucleus undergoes easy reduction to give 4-hydroxyvalerolactone.<sup>218</sup> The method of Rallings and Smith<sup>219</sup> also appears to be successful; this involves the use of palladium strontium carbonate for the reduction of the alkene side chain of 2'-furylalkenes, without affecting the ring. Such compounds as  $\beta$ -2'-furylacrylic esters are exceptions, but the potassium salt of the acid can be selectively reduced in aqueous solution.

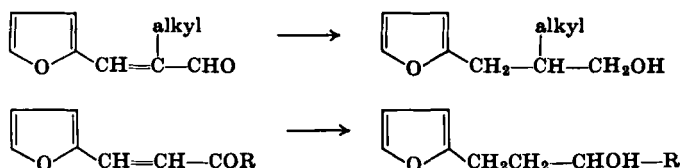
Pt-Al or Cu-Al catalysts at 150° also seem to reduce the side chain selectively<sup>220</sup>:



Similarly<sup>211</sup> with Ni-BeO or Ni-CdO at 175°:



The same authors found that with Cu-Al catalysts similar results were obtained where aldehyde and keto groups are concurrently reduced, with yields of 75–85% and 90–95%, respectively<sup>209</sup>:

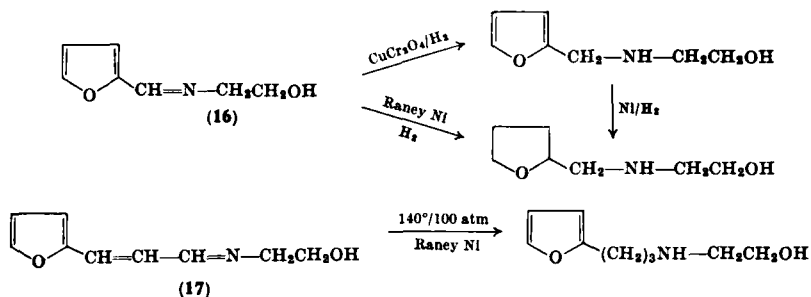


<sup>218</sup> E. Schwenk, D. Papa, H. Hankin, and H. Ginsberg, *Org. Syn.* **27**, 68 (1947).

<sup>219</sup> R. J. Rallings and J. C. Smith, *J. Chem. Soc. (London)* p. 618 (1953).

<sup>220</sup> N. I. Shuikin and I. F. Bel'skii, *Dokl. Akad. Nauk SSSR* **125**, 345 (1959); see *Chem. Abstr.* **53**, 20015 (1959).

Ponomarev<sup>221</sup> selectively reduced the side chain of the azomethines (16) and (17) with copper chromite or Raney nickel:

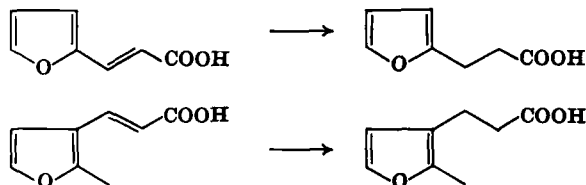


A new kind of hydrogenation in a homogeneous liquid phase, which can be carried out in the presence of cobalt carbonyls at temperatures below  $130^\circ$  with low CO pressure, seems very promising.<sup>222</sup> The following example, which goes almost quantitatively, illustrates this:



The reaction is faster at a carbon monoxide pressure of under 15 atmospheres. Nickel and iron carbonyls show no activity up to at least  $150^\circ$ . In the case of acetylfuran hydrogenolysis occurs. The yield of 2-ethylfuran is 60–70%.

Preliminary studies show that the *diimide reduction* method should be successful:



<sup>221</sup> A. A. Ponomarev, V. Pletneva, V. A. Sedavkina, and L. Barskaya, *Zh. Obshch. Khim.* **24**, 718 (1954); see *Chem. Abstr.* **49**, 5422 (1955).

<sup>222</sup> R. Ercoli and R. E. Torregrosa, *Chim. Ind. (Milan)* **40**, 552 (1958); see *Chem. Abstr.* **53**, 3186 (1959).

Scarpa and Eugster<sup>223</sup> selectively reduced the double bond in 2-furylacrylic acid and 2-methyl-3-furylacrylic acid, with hydrazine/CuSO<sub>4</sub>/air in methanol, to the corresponding furylpropionic acids.

It is worth mentioning that hydrogenolysis can be carried out on O and N functions in the side chain. Isopropylfuryl carbinol is reduced to 2-isobutylfuran in the vapor phase over Pd/Al at 250° in 70–75% yield.<sup>220</sup> Similar results were obtained by the same authors with the metallic Cu/Al catalyst which has already been mentioned. Further examples of hydrogenation to tetrahydrofurans are available.<sup>194, 201, 208, 209, 224–230</sup> Similarly, in the catalytic hydrogenation of furfuryltrimethylammonium salts in the presence of platinum oxide or Raney nickel in ethanol, hydrogenolysis to methyl-tetrahydrofuran and trimethylamine occurs.<sup>231</sup>

The hydrogenolytic Emde degradation applies to 2,5-dimethyl-3-trimethylammoniofuran also (Eugster, unpublished). In contrast, the catalytic reduction of 2,5-dimethyl-3-dimethylaminofuran proceeds normally.<sup>232</sup>

When substituted furans are hydrogenated, ring transformations are also possible. These take place by hydrogenolytic fission of the ring followed by recyclization, e.g.,<sup>233</sup>

<sup>223</sup> J. Scarpa and C. H. Eugster, Unpublished work (1962); cited in J. Scarpa, Dissertation, University of Zürich (1964).

<sup>224</sup> R. M. Lukes and L. S. Nelson, *J. Org. Chem.* **21**, 1096 (1956).

<sup>225</sup> N. I. Chouikin and I. F. Bel'skii, *Bull. Soc. Chim. France* p. 1556 (1956).

<sup>226</sup> N. I. Shuikin and I. F. Bel'skii, *Zh. Obshch. Khim.* **29**, 442 (1959); see *Chem. Abstr.* **53**, 21860 (1959).

<sup>227</sup> N. I. Shuikin and I. F. Bel'skii, *Wiss. Z. Tech. Hochsch. Chem. Leuna-Merseburg* **2**, 129 (1960); see *Chem. Abstr.* **55**, 1567 (1961).

<sup>228</sup> I. F. Bel'skii, N. I. Shuikin, and V. M. Shostakovskii, *Izv. Akad. Nauk SSSR* p. 1631 (1963); see *Chem. Abstr.* **59**, 15241 (1963).

<sup>229</sup> T. Utne, J. D. Garber, and R. E. Jones, U.S. Patent 3,083,236 (1963); see *Chem. Abstr.* **59**, 9985 (1963).

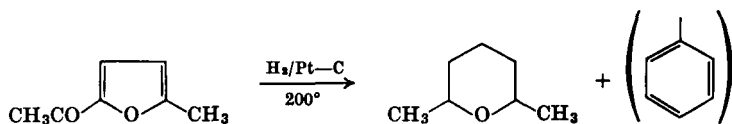
<sup>230</sup> N. I. Shuikin, I. F. Bel'skii, G. K. Vasilevskaya, and V. M. Shostakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.* p. 1475 (1963); see *Chem. Abstr.* **59**, 13915 (1963).

<sup>231</sup> T. Pozzo-Balbi, *Ann. Chim. (Rome)* **45**, 1178 (1955); see *Chem. Abstr.* **51**, 1934 (1957).

<sup>232</sup> C. H. Eugster, Austrian Patent 200,138 (1958); French Patent 1,186,904 (1959).

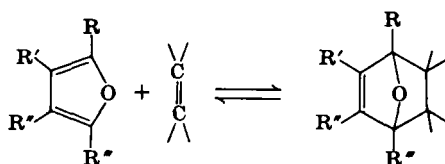
<sup>233</sup> I. F. Bel'skii, N. I. Shuikin, and G. K. Vasilevskaya, *Dokl. Akad. Nauk SSSR* **136**, 591 (1961); see *Chem. Abstr.* **55**, 17629 (1961).





## B. DIELS-ALDER REACTIONS AND RELATED REACTIONS WITH FURANS

A large amount of work has been carried out on diene syntheses involving furans. The most frequent reaction quoted is the "normal" case,



R, R', R'', R''' = H, alkyl, aryl

where the furan forms a bicyclic molecule in a four-center reaction with a dienophile.<sup>1, 28, 46, 71, 83, 134, 135, 164, 167, 234-248</sup> It is remarkable

<sup>234</sup> R. H. Eastman, *J. Am. Chem. Soc.* **72**, 5313 (1950).

<sup>235</sup> N. Clauson-Kaas and N. Elming, *Acta Chem. Scand.* **6**, 560 (1952).

<sup>236</sup> T. Shono and Y. Hachihama, *J. Chem. Soc. Japan, Ind. Chem. Sect.* **56**, 259 (1953); see *Chem. Abstr.* **48**, 10719 (1954).

<sup>237</sup> M. P. Cava, C. L. Wilson, and C. J. Williams, *Chem. Ind. (London)* p. 17 (1955).

<sup>238</sup> M. P. Cava, C. L. Wilson, and C. J. Williams, *J. Am. Chem. Soc.* **78**, 2303 (1956).

<sup>239</sup> J. Sfriso and A. Demeilliers, *Recherches (Paris)* **7**, 36 (1957); see *Chem. Abstr.* **53**, 1295 (1959).

<sup>240</sup> N. Elming, J. T. Nielsen, and N. Clauson-Kaas, U.S. Patent 2,839,539 (1958); see *Chem. Abstr.* **53**, 9248 (1959).

<sup>241</sup> M. P. Cava and M. J. Mitchell, *J. Am. Chem. Soc.* **81**, 5409 (1959).

<sup>242</sup> G. F. D'Alelio, C. J. Williams, and C. L. Wilson, *J. Org. Chem.* **25**, 1025 (1960).

<sup>243</sup> E. Sherman and A. P. Dunlop, *J. Org. Chem.* **25**, 1309 (1960).

<sup>244</sup> Yu. K. Yur'ev, N. S. Zefirov, and M. K. Minacheva, *Zh. Obshch. Khim.* **30**, 3214 (1960); see *Chem. Abstr.* **55**, 19889 (1961).

<sup>245</sup> A. A. Arsenyuk, *Zh. Obshch. Khim.* **31**, 2924 (1961); see *Chem. Abstr.* **59**, 12831 (1962).

<sup>246</sup> H. Krzikalla and H. Linge, *Ber.* **96**, 1751 (1963).

<sup>247</sup> R. Criegee and D. Seebach, *Ber.* **96**, 2704 (1963).

<sup>248</sup> A. A. Ponomarev, *Uch. Zap. Saratovsk. Gos. Univ.* **75**, 51 (1962); see *Chem. Abstr.* **59**, 15240 (1963).

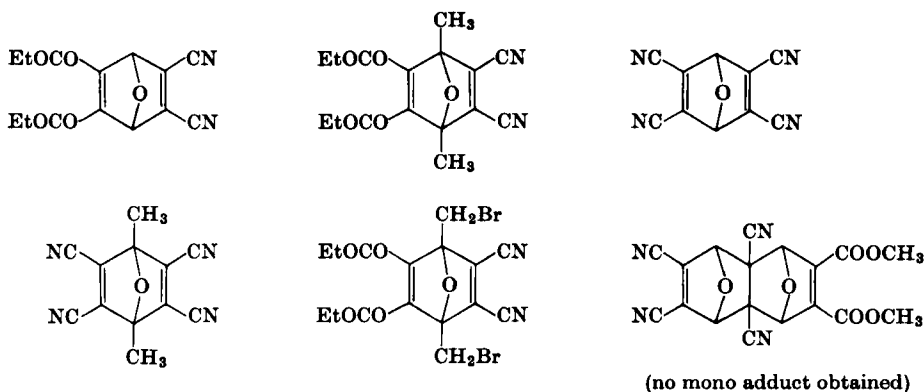
that in many similar additions there is a pronounced reversibility, which is probably due to the fact that the activation energy of such reactions is particularly low. In considering these "normal" additions we shall include only those reactions where a particularly interesting furan or dienophile is involved, or where some aspect of the stereochemistry is clarified.

Recently it has been increasingly recognized that furans can also undergo "abnormal" Diels-Alder reactions.

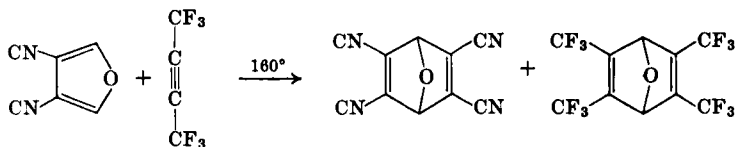
### 1. Simple Normal Addition with Furans

The rule that furans with substituents which show a  $-M$  effect cannot react as diene compounds does not hold with highly active dienophiles. Compounds in this category are acetylene dicarboxylic ester, and particularly dicyanoacetylene.

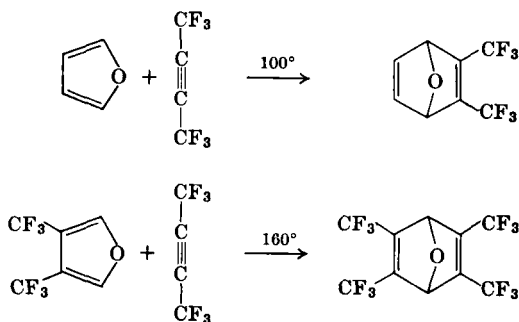
Weis<sup>249</sup> prepared the following adducts (in yields of 50–100%):



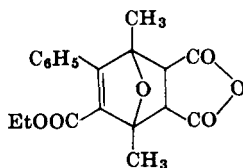
These compounds are colorless, crystalline, and very stable. In contrast, tetracyanoethylene fails to act as a dienophile, and does not react with 3,4-dicyanofuran. The following are further "normal" additions which have been described also by Weis<sup>87</sup>:



<sup>249</sup> C. D. Weis, *J. Org. Chem.* **27**, 3520 (1962).



3-Furoic acids and derivatives react with maleic anhydride to give unstable adducts,<sup>83</sup> e.g.,

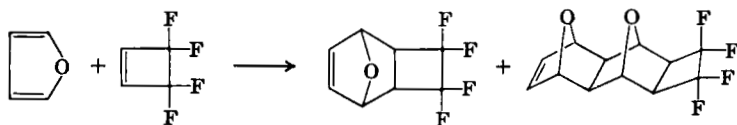


Winslow *et al.*<sup>250</sup> investigated the use of tetracarbethoxyfuran as a diene, and as expected it does not react with maleic anhydride. However, the tetra alcohol, which can be obtained by the  $\text{LiAlH}_4$  reduction, reacts easily. From the point of view of preparative utility, alkoxy- and acetoxyfurans are valuable as dienes. They have recently been obtained relatively easily from 2,5-dialkoxy- or 2,5-diacetoxy-dihydrofurans. The normal products with maleic anhydride, maleimide, fumaronitrile, and dimethylacetylene dicarboxylate have been described.<sup>235, 238, 242, 243</sup> The stereochemistry of the products was not clarified further. Some can be converted into alkoxy- or acetoxyphthalic acids by elimination of the bridge oxygen. These 2-alkoxy- or 2-acetoxyfurans are not very much more reactive than unsubstituted furans, as 2-acetoxyfuran does not react with citraconic anhydride, chloromaleic anhydride, acrylonitrile, *trans*-dibenzoyl ethylene, etc. 3,3,4,4-Tetrafluorocyclobutene adds easily to furan, and the product produced can undergo a second normal furan addition.<sup>251</sup>

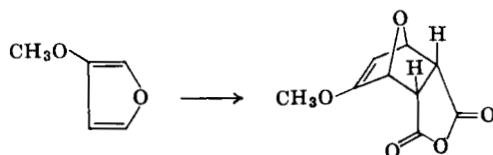
<sup>250</sup> E. C. Winslow, J. E. Masterson, and D. A. Campbell, *J. Org. Chem.* **23**, 1383 (1958).

<sup>251</sup> R. J. Shozda and R. E. Putnam, *J. Org. Chem.* **27**, 1559 (1962).

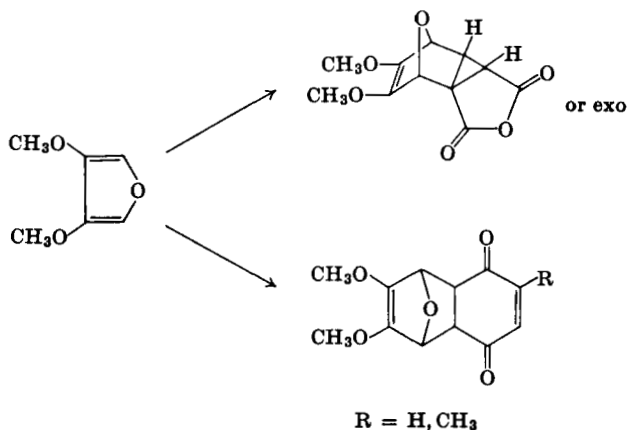
The stereochemistry of the products is not certain.



It is expected that 3-methoxyfuran will show an increased diene activity over unsubstituted furan. The only reported reaction is with maleic anhydride, thus:



to give the normal product, 4-methoxy-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride.<sup>252</sup> 3,4-Dimethoxyfuran shows an unusually high diene activity<sup>170</sup>:

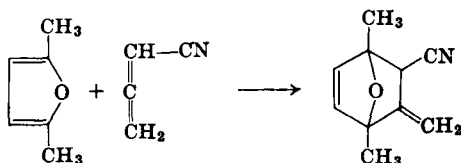


It reacts exothermically to give 4,5-dimethoxy-3,6-epoxy-exo(?)1,2,3,6-tetrahydrophthalic anhydride (which is sterically homogeneous). Similarly, adducts are formed with dimethyl maleate,

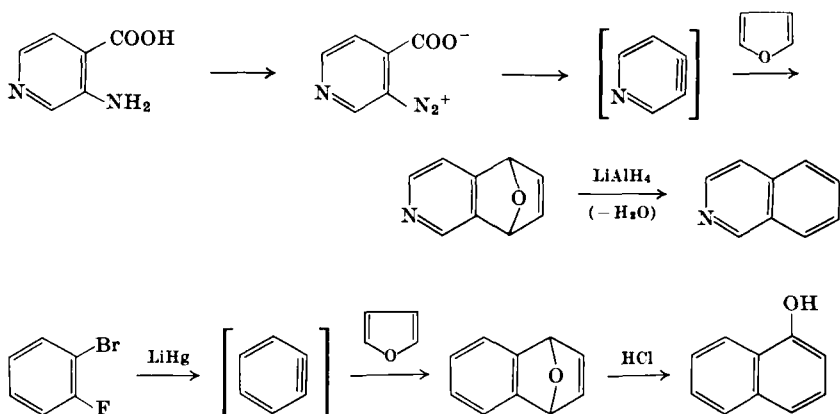
<sup>252</sup> B. E. Fisher and J. E. Hodge, *J. Org. Chem.* **29**, 776 (1964).

acrylonitrile, and methyl acrylate. There is also reaction with benzoquinones, and this is the first normal Diels-Alder reaction of a furan with a quinone.

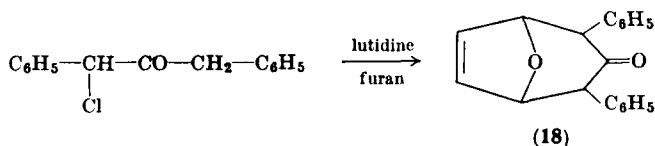
Kurtz *et al.*<sup>253</sup> have shown that an interesting reaction occurs with *allenes*, when an adduct is formed with furans in 87% yield:



Similarly Kauffmann and Boettcher<sup>254</sup> and Wittig and Pohmer<sup>255</sup> have shown that *arynes* are trapped *in situ* by furan. The respective reactions are as follows:



Furan is also suitable for trapping certain intermediates of a *Favorskii* rearrangement<sup>256</sup>:



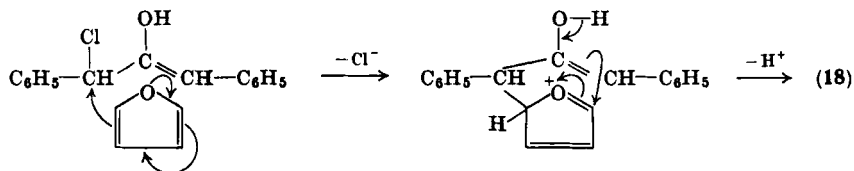
<sup>253</sup> P. Kurtz, H. Gold, and H. Disselnkötter, *Ann.* **624**, 1 (1959).

<sup>254</sup> T. Kauffmann and F.-P. Boettcher, *Ber.* **95**, 949 (1962).

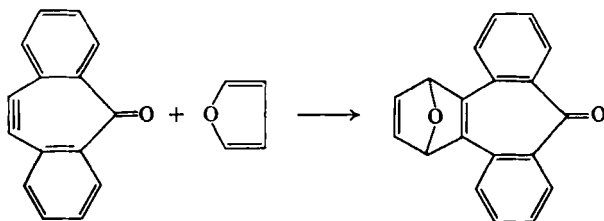
<sup>255</sup> G. Wittig and L. Pohmer, *Ber.* **89**, 1334 (1956).

<sup>256</sup> A. W. Fort, *J. Am. Chem. Soc.* **84**, 4979 (1962).

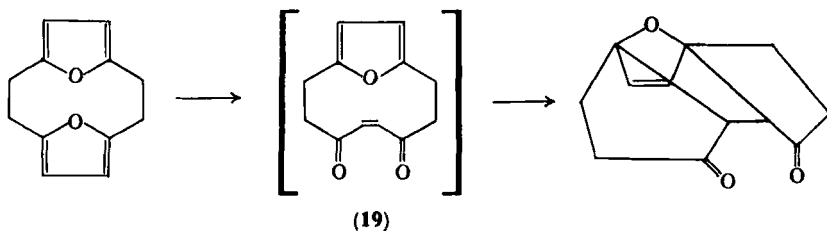
The yield is 18%. A possible alternative interpretation is that furan reacts by the following mechanism:



On the basis of the addition reactions already described in Sections III, B and C, this interpretation is not as improbable as at first might be thought. In this connection the trapping of benzocyclobutadiene<sup>241</sup> and some seven-membered arynes<sup>257</sup> by furan, to give normal adducts, is worth mentioning:



Wasserman and Doumaux<sup>258</sup> observed that an unusual intramolecular Diels-Alder reaction occurred via the photooxidation of a furanoheterocyclophane. The yield was 42%.



The authors suggest that the reaction occurs as the result of the formation of an intermediate (19) where the ring has been hydrolytically opened. They consider that the diene and dienophile are in a

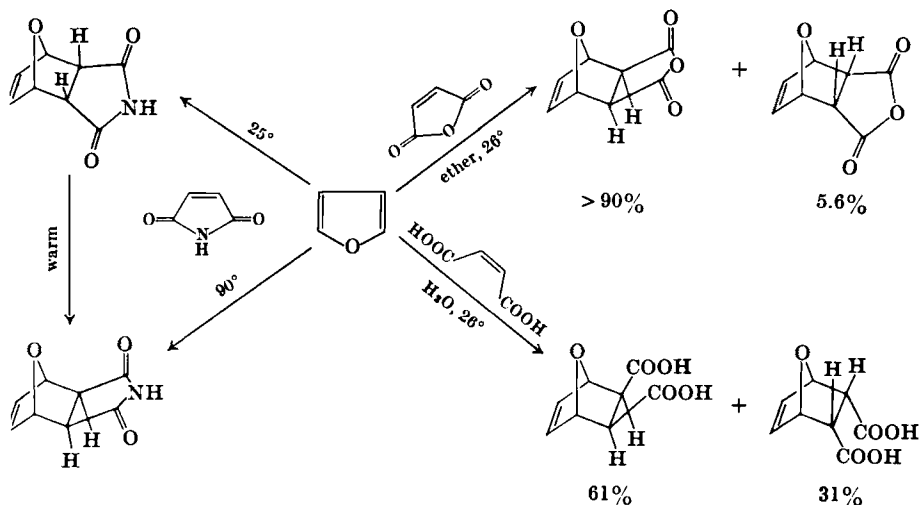
<sup>257</sup> W. Tochtermann, K. Oppenländer, and U. Walter, *Ber.* **97**, 1318 (1964).

<sup>258</sup> H. H. Wasserman and A. R. Doumaux, *J. Am. Chem. Soc.* **84**, 4611 (1962).

sterically favorable position for an intramolecular Diels-Alder reaction.

## 2. The Stereochemistry of the Diene Adducts

Recent work shows that less reactive furans, where longer reaction times and higher temperatures are necessary, give rise to exo adducts. In contrast, with more active dienes, and in reactions at lower temperatures, more endo adducts are formed. It has been shown that the reactions are seldom completely stereospecific. This is illustrated by the work of Stockmann.<sup>259</sup> He employed a new titration technique with hypiodite, and found that the maleic anhydride-furan adduct which was prepared in an ether medium contained about 5-6% of the exo isomer.



The investigations of Kwart and Burchuk<sup>260</sup> on the furan-maleimide system gave similar results. Endo addition is favored kinetically, but the adduct usually changes to the thermodynamically more stable exo adduct. The free energy difference is not more than  $-1.2$  kcal/mole.<sup>261</sup> Berson *et al.* suggest a probable mechanism for the endo $\rightleftharpoons$ exo rearrangement.

<sup>259</sup> H. Stockmann, *J. Org. Chem.* **26**, 2025 (1961).

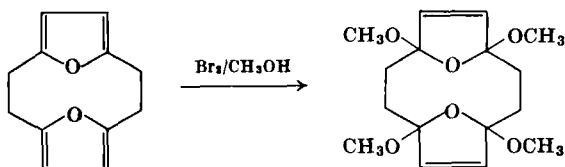
<sup>260</sup> H. Kwart and I. Burchuk, *J. Am. Chem. Soc.* **74**, 3094 (1952).

<sup>261</sup> J. A. Berson and R. Swidler, *J. Am. Chem. Soc.* **75**, 1721 (1953).



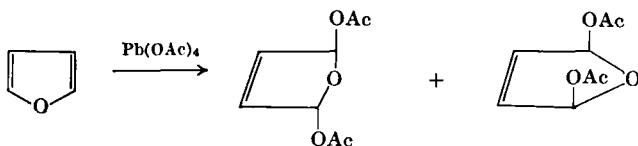


low temperatures with a platinum electrode.<sup>242, 263-269</sup> A review of both methods, and also of the use of 2,5-dialkoxy-2,5-dihydrofurans, is given by Elming.<sup>270</sup> Stereochemically, both methods yield a mixture of *cis* and *trans* isomers. The electrolytically prepared 2,5-dialkoxyfurans contain fewer halogen impurities, and therefore they are more stable than the products from bromomethoxylation. There is a further advantage in the electrolytic method, in that even negatively substituted furans can be alkoxyated. Sulfuric acid can be used in place of the more usual ammonium bromide.<sup>266</sup> Bromomethoxylation is often used as it is a convenient method. Examples are tetraphenylfuran<sup>271</sup> or the previously mentioned furan-cyclophane.<sup>157</sup>



## 2. Oxidation with Lead Tetraacetate

Lead tetraacetate in glacial acetic acid is used for 2,5-acetoxylation of furan derivatives<sup>272</sup>:



<sup>263</sup> N. Clauson-Kaas, F. Limborg, and K. Glens, *Acta Chem. Scand.* **6**, 531 (1952).

<sup>264</sup> N. Clauson-Kaas, *Acta Chem. Scand.* **6**, 569 (1952).

<sup>265</sup> N. Clauson-Kaas, F. Limborg, and P. Dietrich, *Acta Chem. Scand.* **6**, 545 (1952).

<sup>266</sup> N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.* **6**, 551 (1952).

<sup>267</sup> N. Elming, *Acta Chem. Scand.* **6**, 572 (1952).

<sup>268</sup> N. Elming, *Acta Chem. Scand.* **10**, 1664 (1956).

<sup>269</sup> A. A. Ponomarev and I. A. Markushina, *Zh. Obshch. Khim.* **30**, 976 (1960); see *Chem. Abstr.* **55**, 2597 (1961).

<sup>270</sup> N. Elming, *Advan. Org. Chem.* **2**, 67 (1960).

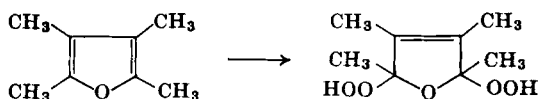
<sup>271</sup> R. E. Lutz and W. J. Welstead, *J. Am. Chem. Soc.* **85**, 755 (1963).

<sup>272</sup> N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.* **6**, 534 (1952).

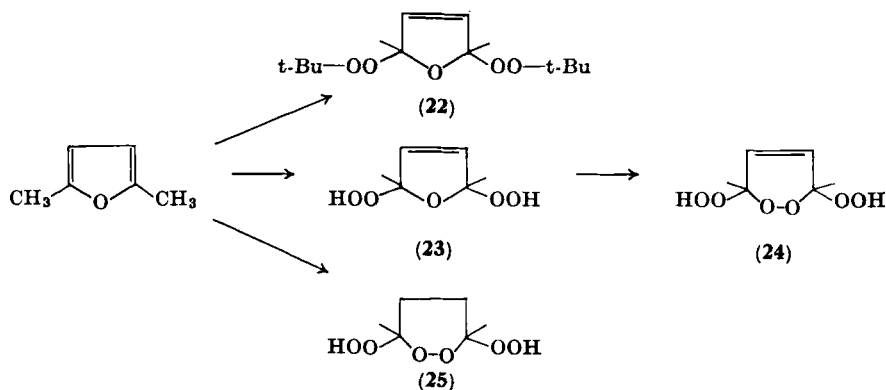
As usual a *cis-trans* isomeric mixture forms, which can be separated by crystallization. 3-Isopropylfuran can be oxidized in a similar way, while 2-substituted furans are resistant to acetoxylation.<sup>273</sup>

### 3. Oxidation with Hydrogen Peroxide

2,3,4,5-Tetramethylfuran forms a uniform bishydroperoxide with hydrogen peroxide<sup>247</sup>:



In contrast the reaction is somewhat more complicated with 2,5-dimethylfuran.<sup>274</sup> This compound reacts similarly with *tert*-butylhydroperoxide to give the homogeneous bisperoxide **22**. However, if the reaction is carried out with 67%  $\text{H}_2\text{O}_2$  in tetrahydrofuran with the addition of dilute sulfuric acid, 2,5-dimethylfuran does give the expected hydroperoxide **23**, but also gives the six-membered ring peroxides **24** and **25**.



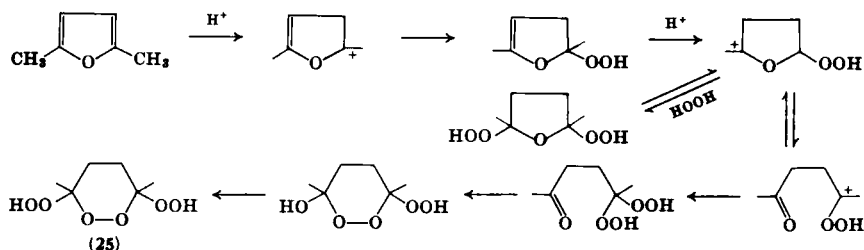
**23** can be converted on ring expansion into **24**, which is extremely explosive, by further treatment of **23** with  $\text{H}_2\text{O}_2$  in the presence of sulfuric acid, and the yield is 80%.

All three peroxides **22**, **24**, and **25** are also formed in different quantities when 2,5-dimethylfuran reacts with  $\text{H}_2\text{O}_2$  at pH 1-3.

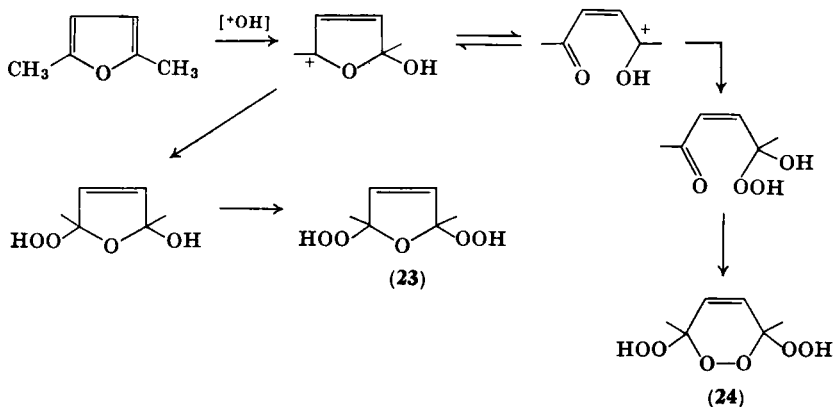
<sup>273</sup> N. Elming, *Acta Chem. Scand.* **6**, 578 (1952).

<sup>274</sup> D. Seebach, *Ber.* **96**, 2712 (1963).

The formation of **24** and **25**, which have saturated and unsaturated rings, from the same starting material seems astonishing at first. Obviously two different but simultaneous reactions occur. The formation of the saturated peroxide **25** is considered by Seebach to go by the following route:

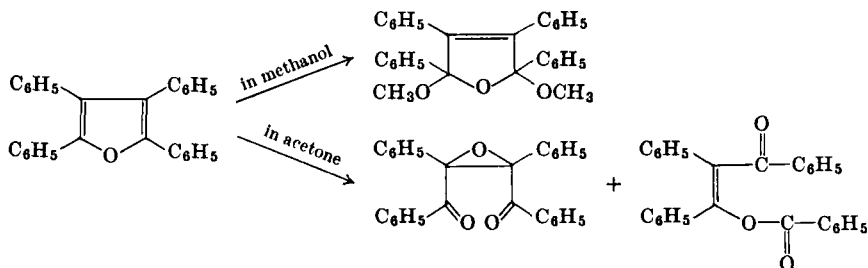


To explain the formation of both unsaturated peroxides **23** and **24** the following mechanism is suggested:

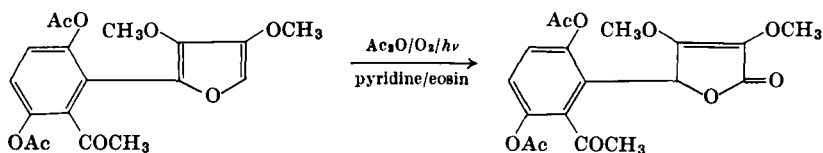


In certain cases, a photochemical 2,5-oxidation can also be carried out. Wasserman and Liberles<sup>275</sup> oxidized tetraphenylfuran in methanolic solution, by irradiation and treatment with atmospheric oxygen, and obtained 2,5-dimethoxy-2,3,4,5-tetraphenyl-2,5-dihydrofuran. In acetone the furan ring is cleaved:

<sup>275</sup> H. H. Wasserman and A. Liberles, *J. Am. Chem. Soc.* **82**, 2086 (1960).



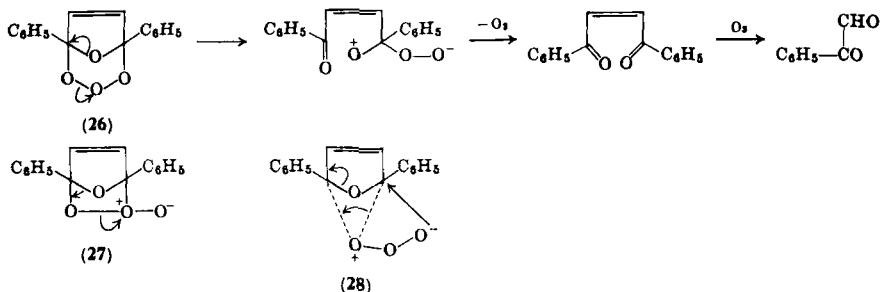
Eugster and Bosshard<sup>174</sup> observed that oxidation to a butenolide occurred under similar conditions:



#### D. ADDITION OF OZONE TO THE FURAN RING

Furan and its derivatives can readily be ozonized, and the ozonides converted into various products.<sup>276, 277</sup>

Bailey and Colomb<sup>278</sup> described an ozonolysis of 2,5-diphenylfuran in methanol-acetone, with two equivalents of ozone, which gave 14% phenylglyoxal and 81% benzoic acid. Abnormal ozonizations such as this can be explained if we consider that the initial step is the normal 2,5-addition of ozone on the furan ring. Then **26** or the primary ozonides **27** or **28** could give the resulting ketonic product:



<sup>276</sup> F. P. Florentine, U.S. Patent 2,793,228 (1957); see *Chem. Abstr.* **51**, 16556 (1957).

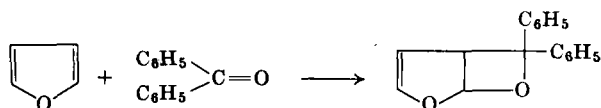
<sup>277</sup> B. P. Jibben and J. P. Wibaut, *Rec. Trav. Chim.* **79**, 342 (1960).

<sup>278</sup> P. S. Bailey and H. O. Colomb, *J. Am. Chem. Soc.* **79**, 4238 (1957).

This interpretation is supported by the ozonolysis of 2,5-diphenylfuran with one mole of ozone, whereby *cis*-1,2-dibenzoylethylene can be isolated in 12% yield.

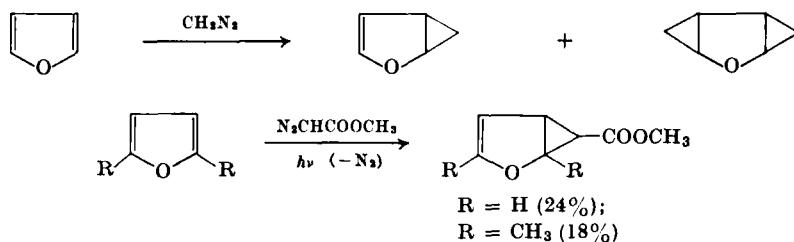
### E. OTHER ADDITIONS

Hammond and Turro<sup>279</sup> recently described a photochemical addition reaction of benzophenone and furan:



The structure of the product is supported by NMR measurements carried out by Gagnaire and Payo-Subiza.<sup>280</sup>

Two further addition reactions to furans are that of diazomethane in the presence of copper bromide<sup>280a</sup> and that of diazoacetic ester:



Schenck and Steinmetz<sup>281</sup> consider that the latter reaction can be explained in terms of a biradical multicenter reaction, with liberation of nitrogen.

Novák and Šorm<sup>282</sup> described an octa-3,5-diene-2,7-dione synthesis. Addition of diazoacetone to 2-methylfuran gave a cyclopropane derivative, which subsequently rearranged:

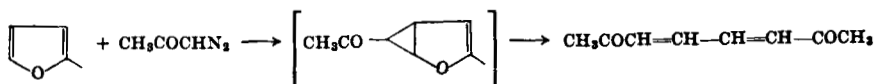
<sup>279</sup> G. S. Hammond and N. J. Turro, *Science* **142**, 1541 (1963).

<sup>280</sup> D. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. France* p. 2623 (1963).

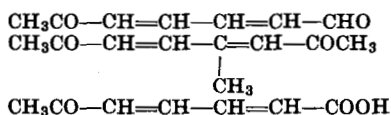
<sup>280a</sup> E. Müller, H. Kessler, H. Fricke, and H. Suhr, *Tetrahedron Letters* p. 1047 (1963).

<sup>281</sup> G. O. Schenck and R. Steinmetz, *Ann.* **668**, 19 (1963).

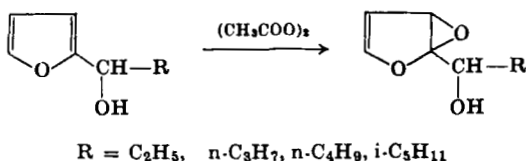
<sup>282</sup> J. Novák and F. Šorm, *Collection Trav. Chim. Czech.* **23**, 1126 (1958).



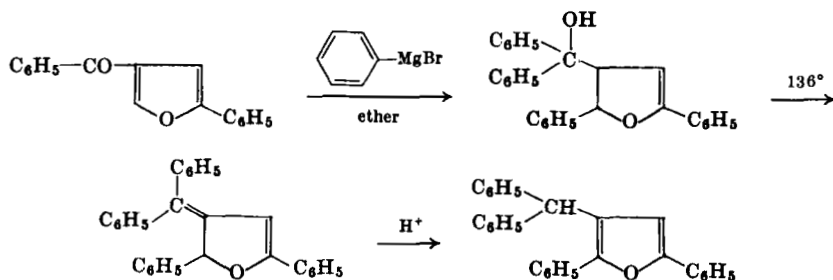
The following were analogously prepared from furan and 2,5-dimethylfuran with diazoacetone or diazoacetic ester:



Azanovskaya and Pensevič-Kolyada<sup>283</sup> oxidized alkylfuryl alcohols to monoepoxides, with acetyl peroxide:



Fuson *et al.*, in the course of their work on Grignard additions to extremely sterically hindered ketones,<sup>284</sup> observed that 2-phenyl-4-benzoylfuran adds a phenyl group at the 5-position of the furan ring as well as to the carbonyl group:



The structure of the product has been confirmed by an independent synthesis.

<sup>283</sup> M. M. Azanovskaya and V. I. Pensevič-Kolyada, *Zh. Obshch. Khim.* **27**, 384 (1957); see *Chem. Abstr.* **51**, 15489 (1957).

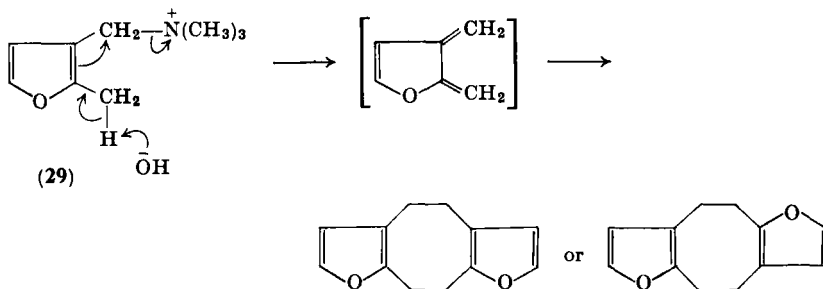
<sup>284</sup> R. C. Fuson, H. S. Killam, and W. S. Smith, *J. Org. Chem.* **27**, 3355 (1962).

## V. Elimination Reactions on the Furan Ring

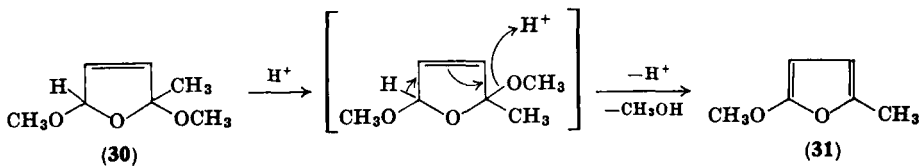
Two elimination processes will be mentioned here which go on at the furan ring and lead to aromatization. The products formed are very reactive, and they can react further to give dimers and polymers.

### A. 1,4-ELIMINATIONS

Winberg and co-workers<sup>157</sup> carried out an interesting Hofmann degradation on 2-methyl-3-furfuryltrimethylammonium hydroxide (29). The dimethylenedihydrofuran so formed is sufficiently reactive to dimerize, but not to polymerize.

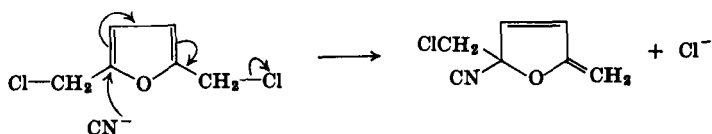


The quaternary ammonium salt (29) was prepared from 2-methyl-3-carbethoxyfuroic acid. Similarly, the acid-catalyzed methanol eliminations from 2,5-dimethoxyfurans are 1,4 elimination processes.<sup>235, 242, 243</sup> They will be discussed in Section VIII.



The following example by Yur'ev *et al.*<sup>285</sup> involves an addition-elimination mechanism:

<sup>285</sup> K. Yu. Novitskii, Yu. K. Yur'ev, and V. N. Zhingareva, *Zh. Obshch. Khim.* **32**, 3303 (1962); see *Chem. Abstr.* **58**, 11301 (1963).



### B. 1,6-ELIMINATIONS

Two examples are known where a Hofmann elimination leads to 2,5-bismethylene compounds.<sup>157, 286</sup> These can undergo further reaction to give heterocyclophanes, in the presence of polymerization inhibitors. If these inhibitors are not present, the dimethylene compound polymerizes.

## VI. Ring Opening Reactions of Furans

Ring cleavage in the furan system is usually obtained by catalytic hydrogenolysis. Examples are given in Section IV of addition reactions, and in Section VII of conversion reactions. Oxidative ring opening has already been described in a part of Section IV.

### A. NONOXIDATIVE RING OPENING

#### 1. Acid-Catalyzed Ring Fission

The acid fission of furans, to yield 1,4-dicarbonyl compounds, is not satisfactory from the preparative point of view. This fission reaction has recently been restudied.<sup>169, 287-292</sup> It is preferable to use the route involving 2,5-dialkoxy-2,5-dihydrofurans, which on hydrogenation and acid hydrolysis give the desired 1,4-dicarbonyl compounds.

Stamhuis *et al.*<sup>293</sup> carried out a kinetic study of the hydrolysis of

<sup>286</sup> D. J. Cram and G. R. Knox, *J. Am. Chem. Soc.* **83**, 2204 (1961).

<sup>287</sup> V. F. Kucherov, *Zh. Obshch. Khim.* **20**, 1885 (1950); see *Chem. Abstr.* **45**, 2928 (1951).

<sup>288</sup> N. Clauson-Kaas and J. T. Nielsen, *Acta Chem. Scand.* **9**, 475 (1955).

<sup>289</sup> V. G. Bukharov and T. E. Pozdnyakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 1108 (1960); see *Chem. Abstr.* **55**, 503 (1961).

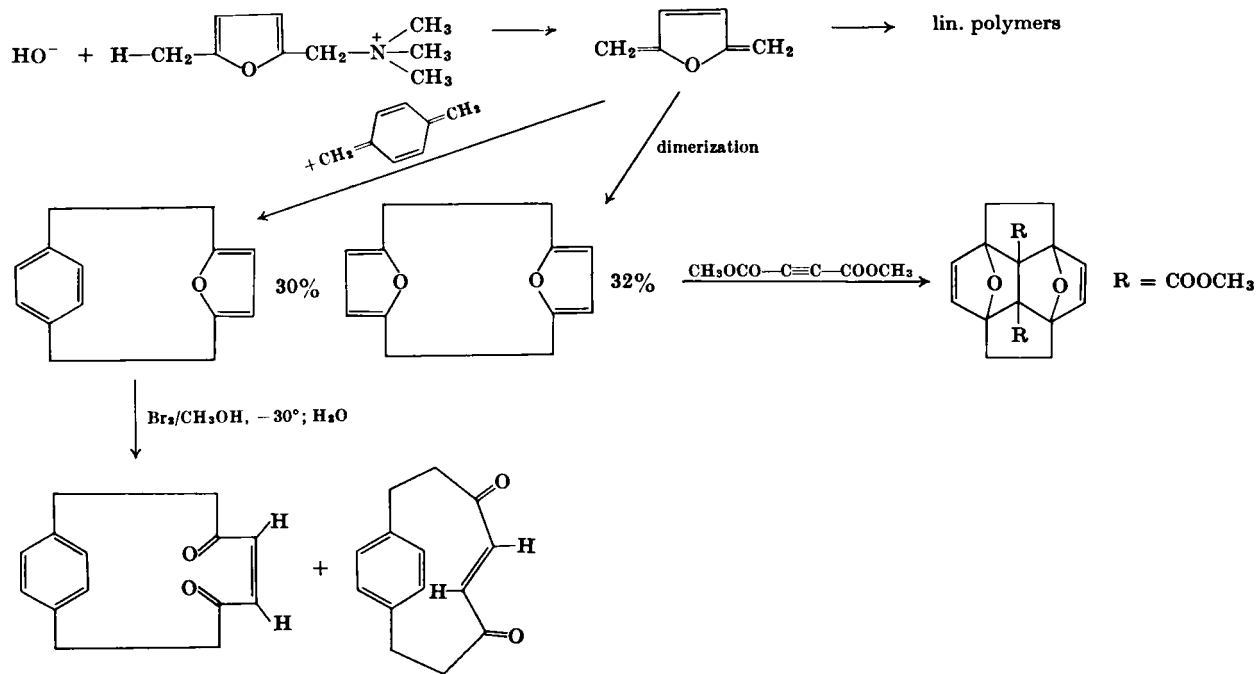
<sup>290</sup> R. Lukeš and J. Šrogl, *Collection Czech. Chem. Commun.* **26**, 2238 (1961).

<sup>291</sup> A. A. Ponomarev and V. A. Sedavkina, *Zh. Obshch. Khim.* **31**, 984 (1961); see *Chem. Abstr.* **55**, 25905 (1961).

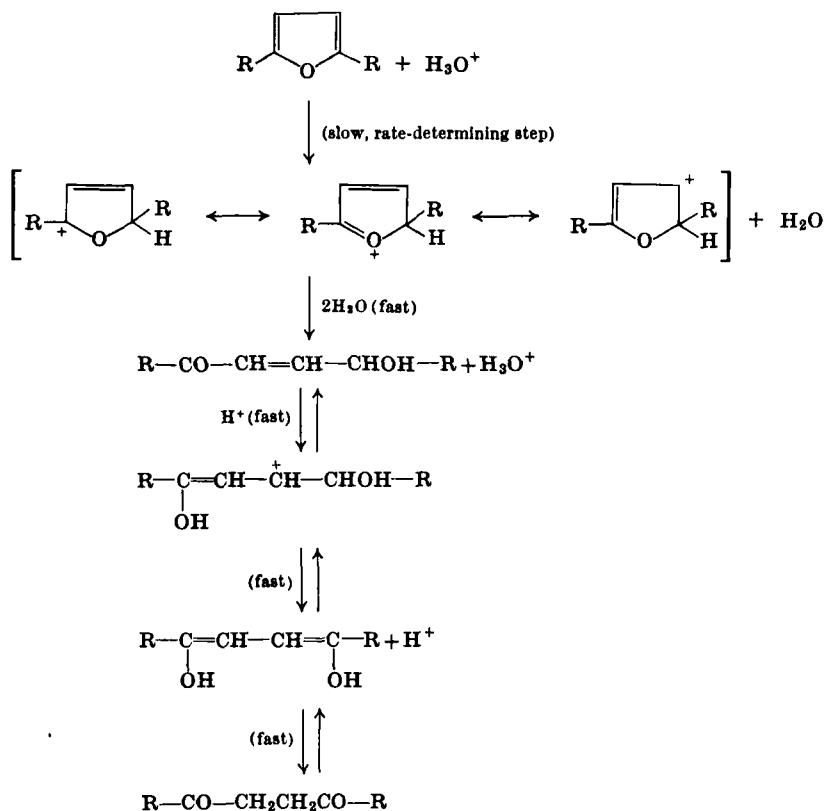
<sup>292</sup> A. A. Ponomarev and V. A. Sedavkina, *Uch. Zap. Saratovsk. Gos. Univ.* **75**, 37 (1962); see *Chem. Abstr.* **59**, 15238 (1963).

<sup>293</sup> E. J. Stamhuis, W. Dreht, and H. Van Den Berg, *Rec. Trav. Chim.* **83**, 167 (1964).





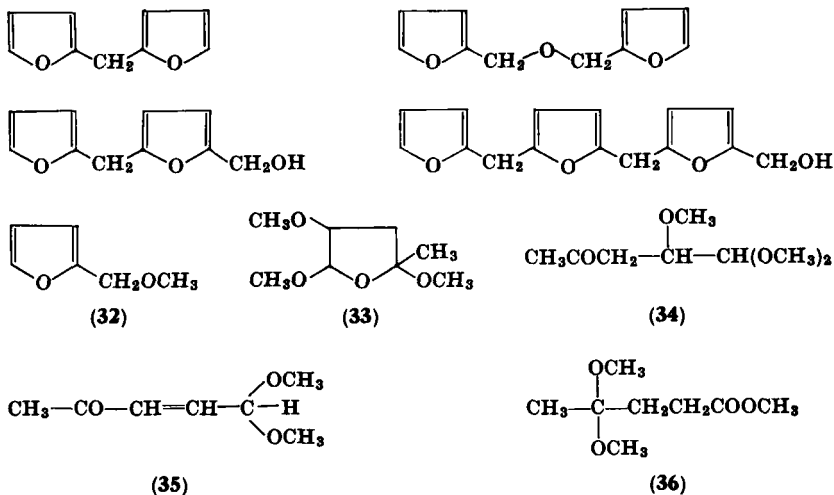
furan and 2,5-dimethylfuran at 25° in aqueous perchloric acid. They showed that the logarithm of the first-order rate constant is linearly dependent upon the Hammett acidity function  $H_0$ . The mechanism must involve protonation at the  $\alpha$ -carbon of the furan ring and not on the O of the ring. This protonation is the rate-determining step, and this then allows nucleophilic attack by the solvent:



A recent extensive investigation has been carried out on furfuryl alcohol, which obviously protonates on the alcohol group and initiates the reaction, which yields levulinic acid.

a. *Furfuryl alcohol.* The fission of furfuryl alcohol in the presence of hydrochloric acid and methanol has been thoroughly studied by

Clauson-Kaas,<sup>288, 294</sup> Lewis,<sup>295</sup> and Birkofer,<sup>296, 297</sup> It was possible to isolate the following compounds in addition to the main product—levulic ester (38)—by careful work-up of the mixture:



Pummerer *et al.*<sup>298, 299</sup> had previously isolated the intermediate 34, but they ascribed a different structure to it. 32, 33, and 34 are intermediates in the formation of levulic ester—long reaction times result in a decrease in the amount of these compounds, and in an increase in the amount of the ester. Birkofer *et al.* considered that the mechanism for the fission, in view of the intermediates formed, was as follows:

Clauson-Kaas and Nielsen<sup>288</sup> obtained similar results when furfuryl alcohol, furfuryl methyl ether, and 2,5-dimethoxy-2,5-dihydro-2-methylfuran were treated with methanolic hydrochloric acid. The following compounds were obtained: 33, 34, 36, 37, and 38, together with at least three further by-products which could not be

<sup>294</sup> N. Clauson-Kaas, *Acta Chem. Scand.* **6**, 556 (1952).

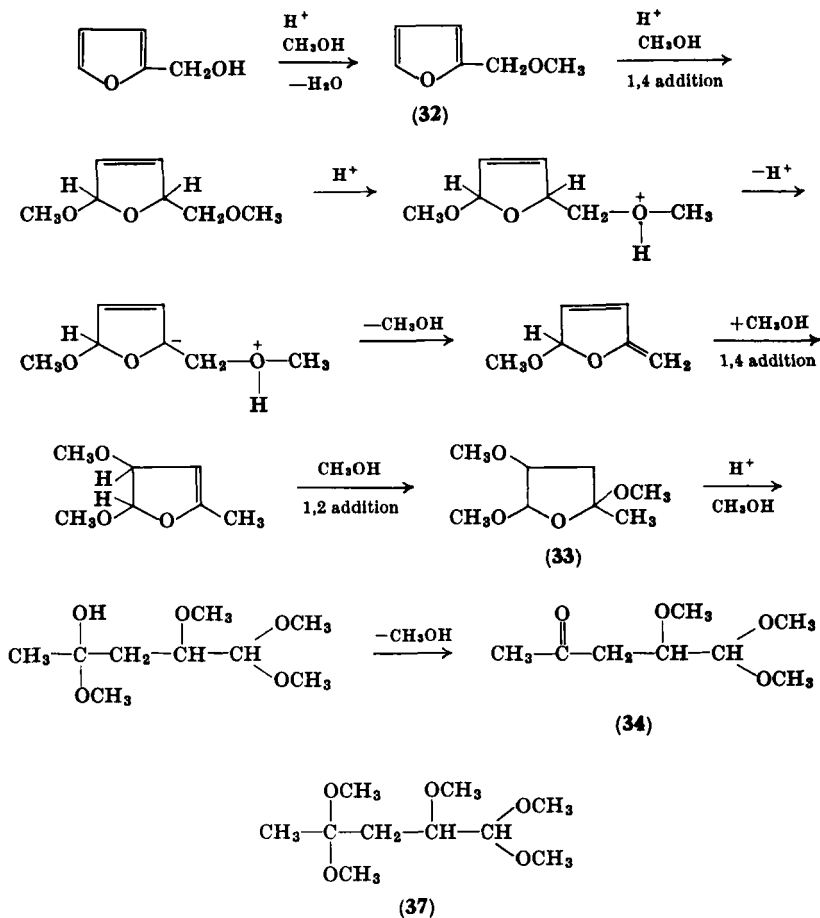
<sup>295</sup> K. G. Lewis, *J. Chem. Soc.* p. 531 (1957).

<sup>296</sup> L. Birkofer and R. Dutz, *Ann.* **608**, 7 (1957).

<sup>297</sup> L. Birkofer and F. Beckmann, *Ann.* **620**, 21 (1959).

<sup>298</sup> R. Pummerer and W. Gump, *Ber.* **56**, 999 (1923).

<sup>299</sup> R. Pummerer, O. Guyot, and L. Birkofer, *Ber.* **68**, 480 (1935).



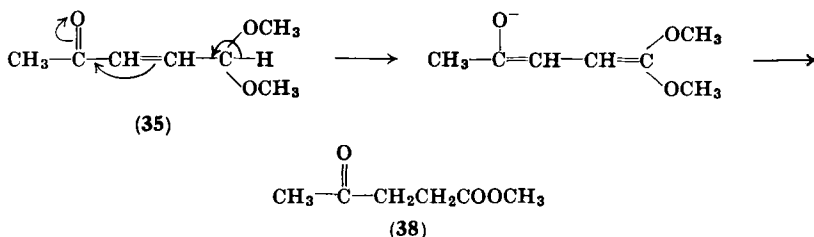
identified. In the case of furfuryl alcohol the following yields were obtained: **33**, 3%; **36**, 1.2%; **34**, 10.1%; **38**, 27.1%.

Lewis<sup>295, 300</sup> considers that the main intermediate in the rearrangement to the  $\gamma$ -ketoacid is the unsaturated acetal **35**, which can give methyl levulate in the following way:

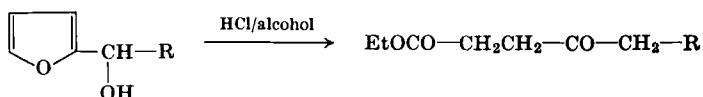
The new intermediate is a ketene-acetal which can be converted into the *ortho* ester with methanol, or into the ester with water.

Substituted furfuryl alcohols (alkylfurylcarbinols) can easily be

<sup>300</sup> K. G. Lewis, *J. Chem. Soc.* p. 4690 (1961).



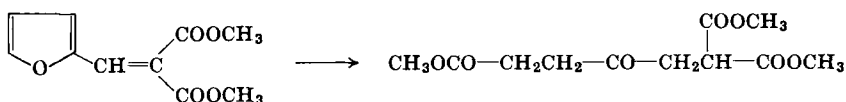
prepared by the Grignard reaction with furfural, and they are very suitable for the preparation of substituted levulic acids, e.g.,



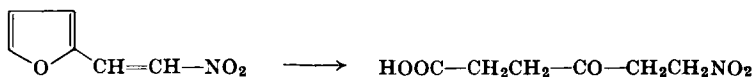
Examples are available.<sup>287, 289, 290-292</sup> The reaction is inherently analogous to the so-called Marckwald reaction.

b. *Acid Fission of Vinyl Furans (Marckwald Reaction)*. The ring fission mechanism for furfuryl alcohol obviously applies to all furans with a vinyl side chain. Rings with free 2-positions upon hydration give rise to derivatives of furfuryl alcohol. An internal oxidation-reduction must subsequently occur, but the mechanism of this cannot definitely be ascertained.

The following recent examples are worth mentioning. Furfurylidene malonic ester can be converted into methyl 2-carbomethoxy-4-ketopimelate<sup>301</sup>:



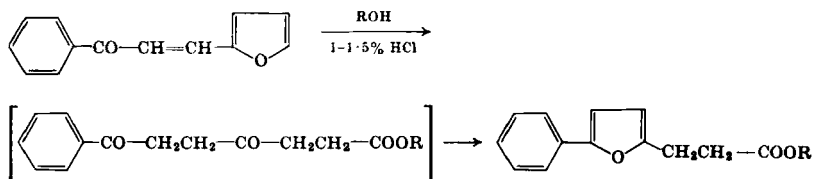
Similarly, 1-nitro-2-(2'-furyl)ethylene yields 4-keto-6-nitrocaproic acid<sup>302</sup>:



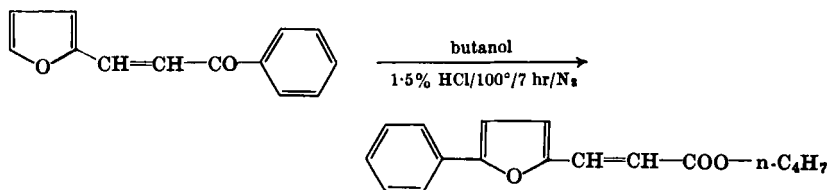
<sup>301</sup> R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.* **74**, 1397 (1952).

<sup>302</sup> C. Grundmann and W. Ruske, *Ber.* **86**, 939 (1953).

In the case of furfurylidene ketones, a furan is again formed, as the result of a secondary ring closure<sup>206</sup>:



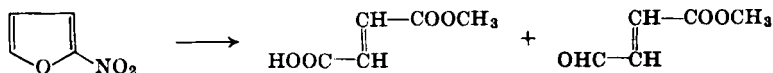
In contrast to the above example, it is reported in a patent<sup>303</sup> that the action of butanol-HCl results in the formation of unsaturated furan derivatives:



Further examples can be found.<sup>290</sup>

## 2. Base-Catalyzed Ring Fission

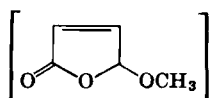
Furans in general can be attacked by nucleophiles, if they are substituted with electron-withdrawing groups (exceptions are the metalation reactions with butyl lithium, etc.). It is possible to cleave 2-nitrofuran with sodium methoxide in methanol, and the reaction yields fumaric acid monoester and methyl-*trans*-3-formylacrylate<sup>304</sup>:



<sup>303</sup> Chemische Werke Witten G.m.b.H., Belgian Patent 622,056 (1962); see *Chem. Abstr.* **59**, 8705 (1963).

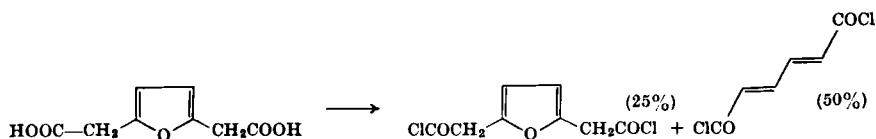
<sup>304</sup> T. Irie, E. Kurosawa, and T. Hamada, *J. Fac. Sci. Hokkaido Univ., Ser. III* **5**, 6; see *Chem. Abstr.* **52**, 16328 (1958).

The reaction probably goes via the following intermediate:



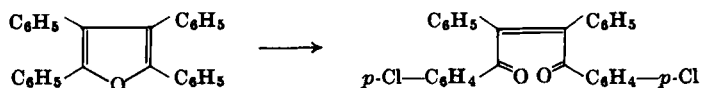
### 3. Different Methods

a. *With Thionyl Chloride.* Novitzkii and co-workers<sup>305</sup> converted furan-2,5-diacetic acid into *trans,trans*-muconic acid dichloride by heating with thionyl chloride in benzene; the furan diacid chloride is obtained as a by-product:



b. *Irradiation with Ultrasonic Waves.* Zechmeister and Wallcave<sup>306</sup> effected a new method of ring fission on 2-bromofuran. It was irradiated with sound waves (of frequency 550–600 kc/sec) in dilute aqueous silver nitrate at 20–25°. Silver bromide was formed together with 0.4% diacetylene and 5.3% acetylene.

c. *With Phosphorus Pentachloride.* On heating with phosphorus oxychloride and phosphorus pentachloride, tetraphenylfuran undergoes ring fission, with the formation of a derivative of dibenzoyl-ethylene<sup>55</sup>:



### 4. Ring Fission of 2-Furoyloximes

The tosylate of 2-furylmethylketoxime (39a) undergoes a ring opening reaction at room temperature, in aqueous ethanol (or methanol), to give the diethyl (or dimethyl) acetal of *cis*-hex-2-ene-1-al, 4,5-dione (40a)<sup>307</sup>:

<sup>305</sup> K. Yu. Novitskii, Yu. K. Yur'ev, V. N. Zhingareva, and M. S. Yunusov, *Zh. Obshch. Khim.* **33**, 2164 (1963); see *Chem. Abstr.* **59**, 13913 (1963).

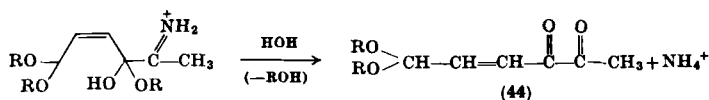
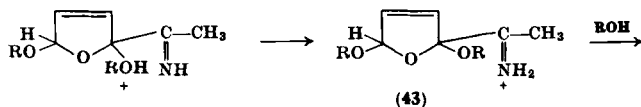
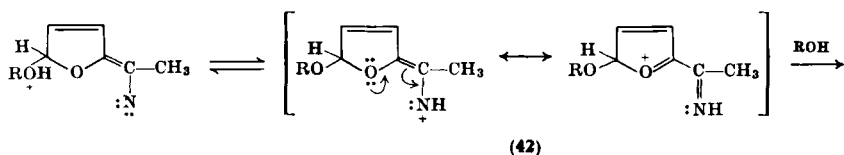
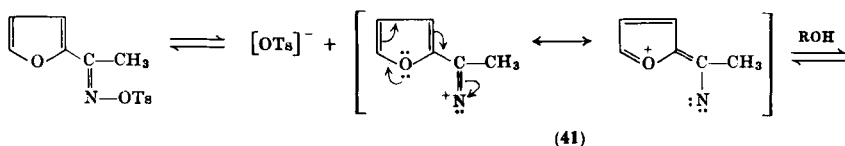
<sup>306</sup> L. Zechmeister and L. Wallcave, *J. Am. Chem. Soc.* **77**, 2853 (1955).

<sup>307</sup> L. Vargha, J. Ramonezai, and P. Bite, *J. Am. Chem. Soc.* **70**, 371 (1948).





This is followed by the attack of the alcohol on the mesomeric cation (41). The next step involves an intramolecular redox reaction, in which the nitrogen is reduced and the ring oxidized. The addition of alcohol and the redox reaction are repeated on the cation (42). The acetal ring of 43 is cleaved and the end product 44 obtained by hydrolysis:



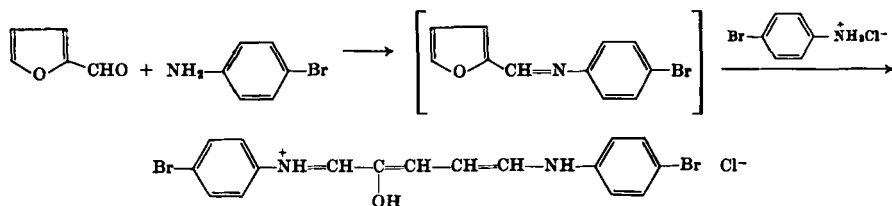
This mechanism is in agreement with the recent work of Vargha and co-workers.<sup>307, 308</sup> The main factor upon which the ring opening reaction is dependent is the stability of the cation 41.

The stereospecificity of the ring opening reaction also supports the mechanism suggested. Models show that in *anti*-furylketoximes the three double bonds, i.e., the double bonds of the furan ring and of the oxime, if considered to be planar, would not be sterically hindered. The prerequisite for the ring opening reaction is then fulfilled. For the *syn* isomers, the three double bonds in the model can only be made planar when the oxygen atom in the ring and the oxime oxygen are in close proximity. This would result in electrostatic repulsion. In this case, therefore, the double bonds are probably not planar, which means that in the *syn* isomers the ring opening requirement is not fulfilled.

<sup>308</sup> L. Vargha and G. Ocskay, *Tetrahedron* 2, 151 (1958).

5. *Fission of the Schiff's Bases of Furfural (Stenhouse Reaction)*

Ring opening in this case is illustrated by a recent example<sup>309</sup> which goes in 86% yield:

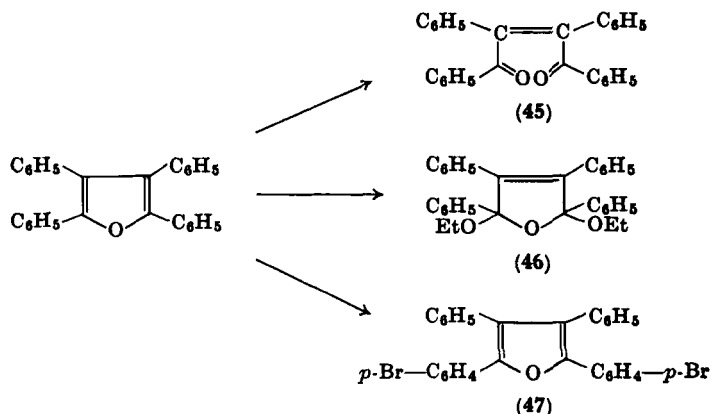


## B. OXIDATIVE RING FISSION

1. *With Bromine*

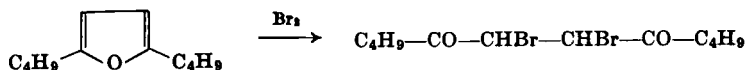
2,5 Oxidation of the furan ring occurs exceptionally easily with halogens. This reaction was described in Section IV, and further examples are available in the literature.<sup>135, 136, 286</sup>

Lutz and Welstead<sup>65</sup> described an anomalous reaction. If tetraphenylfuran is treated with bromine in ethanol-ether, the expected addition product (46) is obtained. However, if ether alone is used, the dibenzoyl ethylene derivative (45) forms. Finally, if tetraphenylfuran in ether is treated with an excess of bromine, the authors found that 47 was produced, nuclear bromination having taken place:



<sup>309</sup> C. V. Brouillette, W. M. Foley, and H. McKennis, *J. Am. Chem. Soc.* **76**, 4617 (1954).

Brown and Wright<sup>131</sup> and Hillers and Berzins<sup>135</sup> found that the reactions of aliphatically substituted furans were analogous:

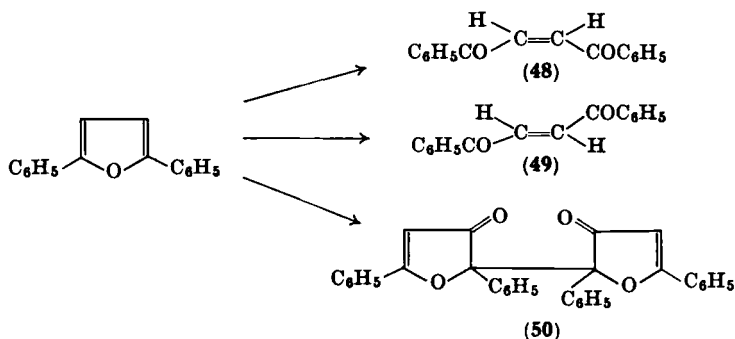


## 2. With Peroxides

The oxidation of substituted furans by hydrogen peroxide is a complex reaction. The products formed include maleic and fumaric acids and saturated dicarboxylic acids.<sup>310-312</sup>

According to Midorikawa,<sup>310</sup> treatment of 2-furylacrylic acid with 35% hydrogen peroxide in dilute hydrochloric acid yields 1,4-pentadiene-3-one-1,5-dicarboxylic acid in 50% yield.

Lutz and Chi-Kang Dien<sup>313</sup> isolated three products from the oxidation of 2,5-diphenylfuran with 30% hydrogen peroxide in glacial acetic acid:



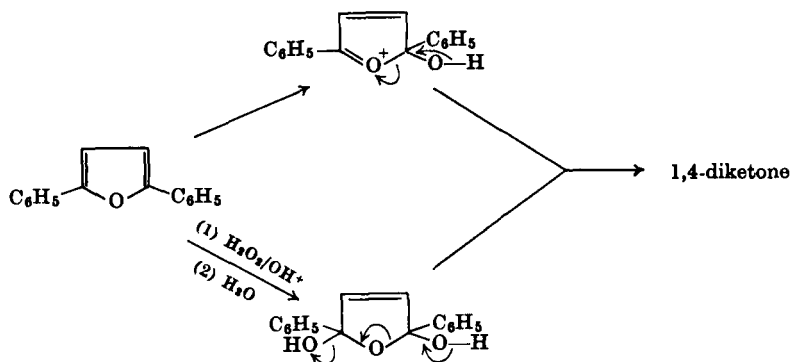
The yields were **48**, 30%; **49**, 14%; and **50**, 4.5%. The *cis* compound isomerizes slowly to the *trans* isomer and under more drastic conditions the *trans* compound is obtained in higher yield. The authors suggest that the first step in the oxidation involves electrophilic attack in the 2-position by the hydrogen peroxide, which gives rise to two intermediates, either of which can lead to the same 1,4-diketone:

<sup>310</sup> H. Midorikawa, *Bull. Chem. Soc. Japan* **26**, 302 (1953); see *Chem. Abstr.* **49**, 998 (1955).

<sup>311</sup> A. P. Salchinkin, L. B. Lapkova, and A. P. Arestenko. *Zh. Prikl. Khim.* **28**, 216 (1955); see *Chem. Abstr.* **49**, 7545 (1955).

<sup>312</sup> A. P. Salchinkin, *Zh. Prikl. Khim.* **32**, 1605 (1959); see *Chem. Abstr.* **53**, 21860 (1959).

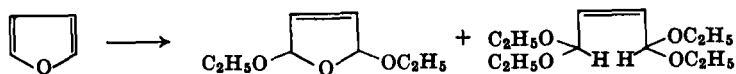
<sup>313</sup> R. E. Lutz and Chi-Kang Dien, *J. Org. Chem.* **23**, 1861 (1958).



The authors consider that compound **50** is produced as the result of oxidation at C-3 with subsequent dimerization.

### 3. Via Electrolytic Oxidation

When electrolytic oxidation is carried out using the technique of Clauson-Kaas, addition does not occur exclusively in the 2,5-position, but ring cleavage of the furan can also take place. This is illustrated by the electrolytic alkoxylation described by the same authors<sup>264</sup>:



A further example of electrolytic oxidation is the conversion of furfural into succinic acid in 37% yield.<sup>314</sup>

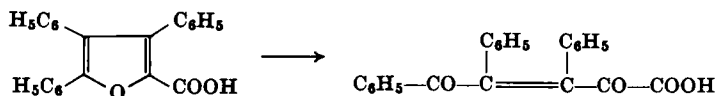
### 4. With Nitric Acid

Furan derivatives undergo ring opening with nitric acid. Thus, 2,5-bis(chloromethyl)furan<sup>315</sup> yields the normal 2,5 addition product with a mixture of nitric acid and acetic anhydride at  $-6^\circ$ . This is converted into maleyl dichloride by distillation. The mechanism of the reaction is not understood.

The fission of 3,4,5-triphenylfuran carboxylic acid by acetic acid-nitric acid at room temperature is worth mentioning<sup>74</sup>:

<sup>314</sup> M. Taniyama, *Toho-Reiyon Kenkyû Hôkoku* **1**, 40 (1954); see *Chem. Abstr.* **53**, 4248 (1959).

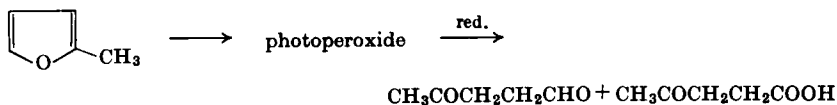
<sup>315</sup> K. Yu. Novitskii, V. P. Volkov, Yu. M. Il'ina, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **33**, 1145 (1963); see *Chem. Abstr.* **59**, 11394 (1963).



Bailey and Hakki<sup>316</sup> cleaved 2,3,5-triphenylfuran with acetic acid-nitric acid and obtained 1-phenyl-1,2-dibenzoyl-2-phenylethylene in 74% yield.

### 5. Photochemical Ring Opening

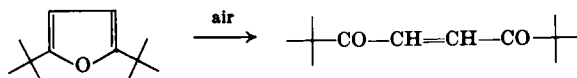
The furan ring can also be opened in oxygen or oxygen-containing gases, often in the presence of eosin and irradiation with light.<sup>275</sup> The structure of the peroxide is usually unknown. 2-Methylfuran undergoes fission by this method to give levulinic aldehyde in 40% yield, with a small quantity of levulinic acid<sup>317</sup>:



Under similar conditions 2,5-dimethylfuran is ring-opened to acetylacetone.

### 6. Via Air Oxidation

2,5-Di-*tert*-butylfuran can be transformed into 1,2-diacyl-ethylene<sup>131</sup>:



## VII. Conversion of Furans into Other Systems

It has been known for a considerable time that furan derivatives can be converted into a large number of different compounds. Only the reactions which have been carried out recently will be described in detail. The conversion of furan derivatives into other heterocyclic systems is usually expected when the labile oxygen system is transformed into a more stable heterocycle.

<sup>316</sup> P. S. Bailey and W. W. Hakki, *J. Am. Chem. Soc.* **71**, 2886 (1949).

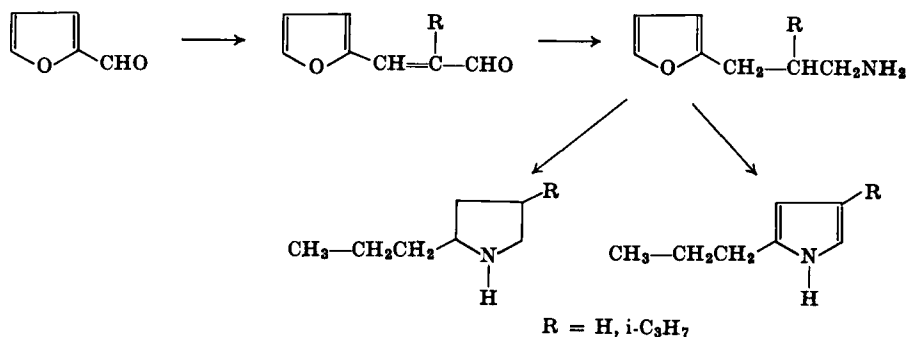
<sup>317</sup> G. O. Schenck, German Patent 881,193 (1953); see *Chem. Abstr.* **50**, 5035 (1956).

## A. INTO PYRROLE DERIVATIVES

Schwanert<sup>318</sup> in 1860 observed probably the first conversion of furan derivatives into those of pyrrole. This reaction has been fully described,<sup>1</sup> and is best carried out nowadays in the gas phase. Thus, furan or one of its derivatives is heated with ammonia or a primary amine to 400–450°, in the presence of activated aluminum oxide or aluminum silicate. The yield varies between 30 and 50% in most cases.<sup>319–324</sup>

Bel'skii<sup>325</sup> succeeded in converting furfural and furfurylidene acetaldehyde into pyrrole at 300° and pyrrolidine homologs at 200°, by reductive amination on Raney nickel, which was followed by rearrangement in the gas phase, in the presence of Pt:

Another example is provided by the work of Eastman and Detert<sup>326</sup>



<sup>318</sup> H. Schwanert, *Ann.* **116**, 257 (1860).

<sup>319</sup> Yu. K. Yur'ev and E. G. Vendel'shtein, *Zh. Obshch. Khim.* **21**, 259 (1951); *Chem. Abstr.* **45**, 7564 (1951).

<sup>320</sup> Yu. K. Yur'ev and E. G. Vendel'shtein, *Zh. Obshch. Khim.* **23**, 2053 (1953); see *Chem. Abstr.* **49**, 3120 (1955).

<sup>321</sup> Yu. K. Yur'ev, *Vopr. Ispol'z. Pentozansoderzh. Syr'ya Tr. Vses. Soveshch. Riga*, 1955 p. 405 (1958); see *Chem. Abstr.* **53**, 14078 (1959).

<sup>322</sup> H. Sugisawa and K. Aso, *Tohoku J. Agr. Res.* **10**, 137 (1959); see *Chem. Abstr.* **54**, 11015 (1960).

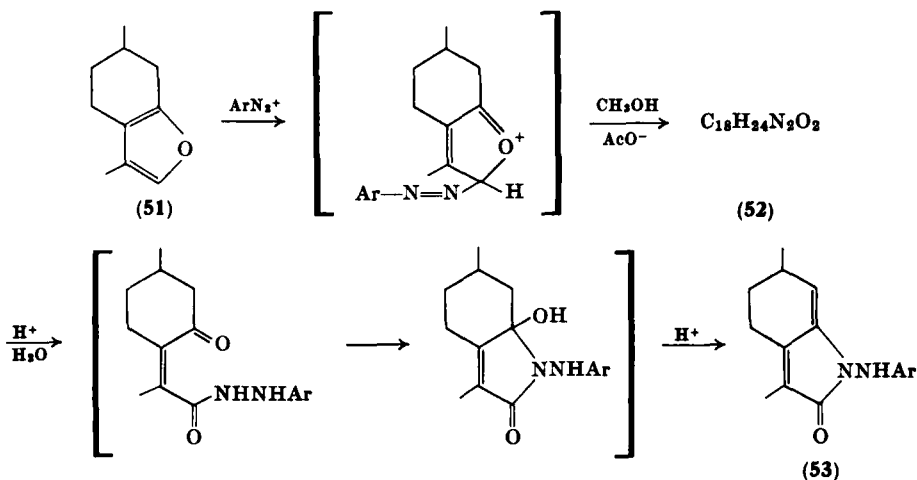
<sup>323</sup> I. F. Bel'skii and N. I. Shuikin, *Dokl. Akad. Nauk SSSR* **137**, 331 (1961); see *Chem. Abstr.* **55**, 19894 (1961).

<sup>324</sup> H. Sugisawa and K. Aso, *Nippon Nogei Kagaku Kaishi* **33**, 259 (1959); see *Chem. Abstr.* **59**, 8695 (1963).

<sup>325</sup> I. F. Bel'skii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 1077 (1962); see *Chem. Abstr.* **57**, 12410 (1962).

<sup>326</sup> R. H. Eastman and F. L. Detert, *J. Am. Chem. Soc.* **73**, 4511 (1951).

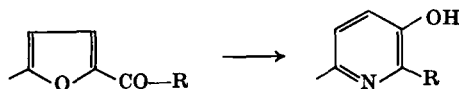
on 4,5,6,7-tetrahydro-3,6-dimethylbenzofuran (51). This can be converted by *p*-toluene diazonium sulfate into a 2-pyrrolone derivative (53), via an intermediate (52), the structure of which has not been conclusively proved:



## B. INTO PYRIDINE DERIVATIVES

### 1. From 2-Acylfurans

Furyl-2-ketones on heating with ammonia yield 2-substituted 3-hydroxypyridines:



This reaction is well known,<sup>1</sup> and there are a number of new examples.<sup>252, 322, 327-331</sup> The by-products can be 2-acylpyrroles<sup>332</sup>:

<sup>327</sup> H. Leditschke, *Ber.* **85**, 202 (1952).

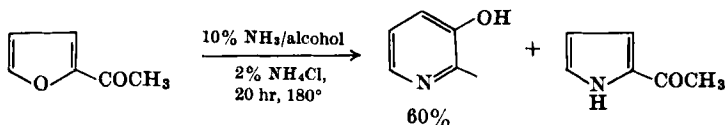
<sup>328</sup> H. Leditschke, *Ber.* **86**, 123 (1953).

<sup>329</sup> W. Gruber, *Can. J. Chem.* **31**, 564 (1953); see *Chem. Abstr.* **47**, 12383 (1953).

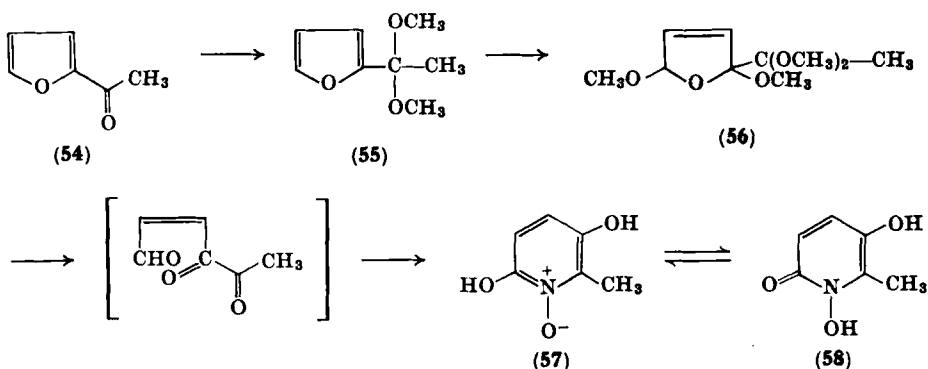
<sup>330</sup> L. D. Smirnov, K. M. Dyumaev, N. I. Shuikin, and I. F. Bel'skii, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 2246 (1962); see *Chem. Abstr.* **58**, 10163 (1963).

<sup>331</sup> L. D. Smirnov, S. I. Sholina, K. E. Kruglyakova, and K. M. Dyumaev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* p. 890 (1963); see *Chem. Abstr.* **59**, 8698 (1963).

<sup>332</sup> H. Sugisawa and K. Aso, *Chem. Ind. (London)* p. 887 (1958).



Clauson-Kaas and co-workers<sup>333</sup> have carried out a different pyridine synthesis with acylfurans. 2-Acetylfuran (**54**) is first converted into the ketal (**55**). After electrolysis to **56**, the pyridine-*N*-oxide (**57**) is formed via acid-catalyzed ring opening and treatment with hydroxylamine. A tautomeric pyridone form (**58**) (hydroxamic acid) has also been proposed<sup>334</sup>:



## 2. From Furfurylamines

In a similar way it is possible to obtain pyridine derivatives from furfurylamines, via 2,5 oxidation.<sup>335-338</sup> Thus, furfurylamine can be converted into 3-hydroxypyridine.

Clauson-Kaas<sup>337</sup> worked out a vitamin B<sub>6</sub> synthesis on the basis of this method. Furan is converted by an Alder-Rickert reaction into furan-3,4-dicarboxylic ester, which is in turn converted into pyridoxine, according to the following scheme:

<sup>333</sup> J. T. Nielsen, N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand.* **9**, 9 (1955).

<sup>334</sup> J. T. Nielsen, N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand.* **9**, 30 (1955).

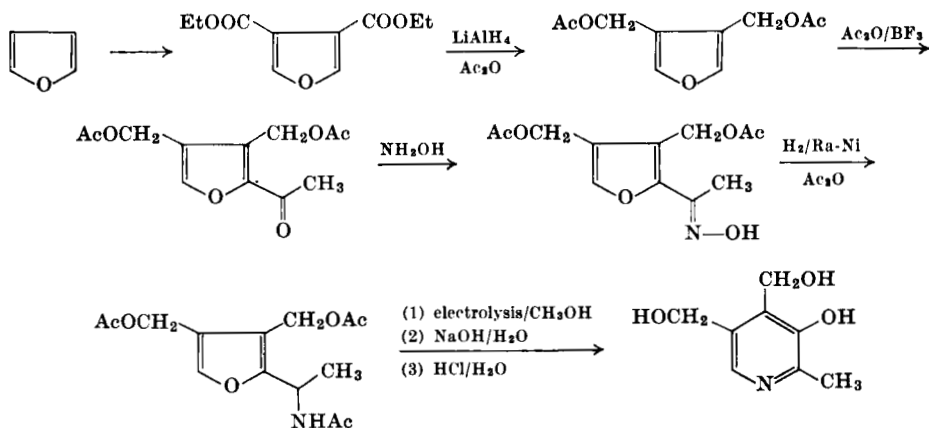
<sup>335</sup> N. Clauson-Kaas and P. Nedenskov, *Acta Chem. Scand.* **9**, 14 (1955).

<sup>336</sup> P. Nedenskov, N. Elming, J. T. Nielsen, and N. Clauson-Kaas, *Acta Chem. Scand.* **9**, 17 (1955).

<sup>337</sup> N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.* **9**, 23 (1955).

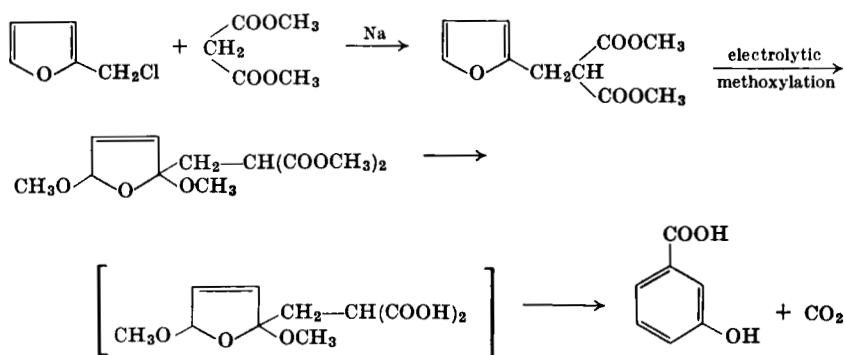
<sup>338</sup> N. Elming, N. Clauson-Kaas, and Z. Tyle, *Acta Chem. Scand.* **9**, 1 (1955).





## C. INTO BENZENE DERIVATIVES

Furans with suitable substituents in the 2-position can also be converted into phenols. These can be transformed into a 1,4-dicarbonyl system by 2,5 oxidation and ring opening. This system can then condense intramolecularly into a six-membered ring.<sup>339, 339</sup> The synthesis of *m*-hydroxybenzoic acid in 26% yield from furfuryl chloride<sup>268</sup> is an example of this:



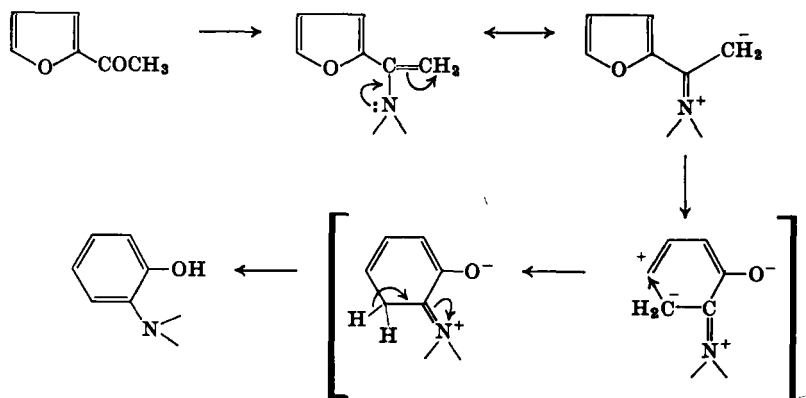
An interesting reaction is the “*o*-aminophenol rearrangement” of acylfuran-enamines described by Birkofer and Daum.<sup>340</sup> 2-Acylfurans condense with secondary amines in the presence of a small quantity

<sup>339</sup> N. Clauson-Kaas and P. Nedenskov, *Acta Chem. Scand.* **9**, 27 (1955).

<sup>340</sup> L. Birkofer and G. Daum, *Ber.* **95**, 183 (1962).

of glacial acetic acid, with elimination of water, to give enamines. On distillation the enamines undergo ring expansion to 2-aminophenols.

The rearrangement can be explained on the basis of the tendency with which the relatively unstable furan ring is converted into a more stable aromatic system. The authors propose the following mechanism:

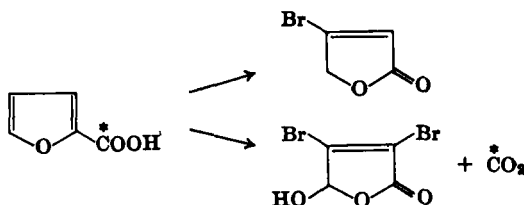


#### D. INTO BUTENOLIDES

##### 1. Conversions of Simple Furan Derivatives

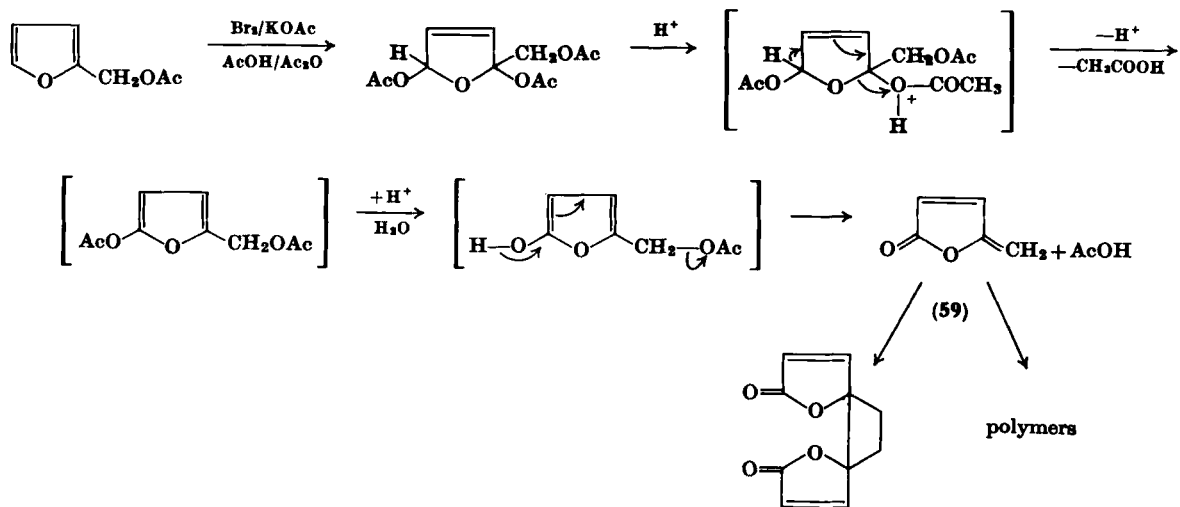
The well-known conversion of certain furans into lactones has been further studied recently. 2-Furoic acid, which was labeled in the carboxyl group, gave radioactive  $\text{CO}_2$  when oxidized by bromine water to mucobromic acid.<sup>341</sup>

Under specific conditions  $\beta$ -bromocrotonolactone can be obtained in small quantities from 2-furoic acid<sup>342</sup>:



<sup>341</sup> W. J. Gensler, E. Smakula, and A. L. Bluhm, *J. Am. Chem. Soc.* **77**, 2890 (1955).

<sup>342</sup> T. J. Mabry, *J. Org. Chem.* **28**, 1699 (1963).

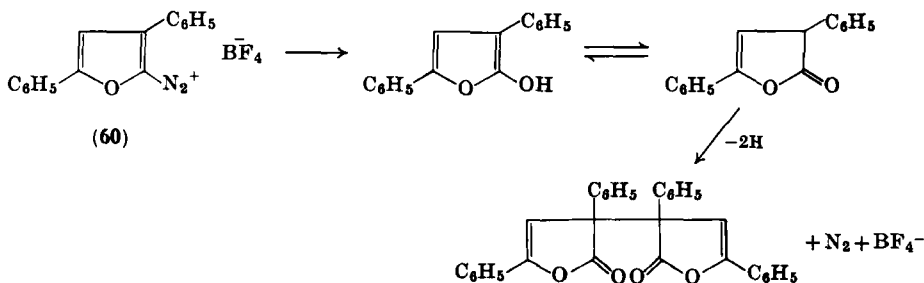


D'Alelio *et al.*<sup>242</sup> converted furfuryl acetate into protoanemonin (59) and its dimer (anemonin) via several intermediates, which were not isolated.

A similar lactone was prepared previously by Gilman and co-workers.<sup>343</sup> Oxidation of 2-acetoxymethylfurans with bromine yields an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone. When the reaction is carried out in carbon tetrachloride a  $\gamma$ -bromobutenolide forms, while in a mixture of acetic acid and acetic anhydride solvolysis occurs, with the formation of  $\gamma$ -acetoxymethylbutenolide.<sup>242</sup>

The latter was prepared by Elming and Clauson-Kaas,<sup>344</sup> by using lead tetraacetate in acetic acid.

Ried and Bodenstedt<sup>345</sup> obtained an interesting  $\alpha,\beta$ -unsaturated butenolide, when the diazofuran (60) was warmed with water. It is possible that the  $\alpha$ -hydroxy derivative forms first, which then dimerizes at the  $\beta$ -position in its keto form. The reaction might proceed by a radical mechanism.



## 2. Conversions of *O*-Furylacetylbenzoquinones

The compounds already mentioned in Section III, C can be oxidized by different methods in their leucoacetate form, which is stable and can easily be crystallized. It was not possible to transform the furan ring into a 1,4-dicarbonyl structure, because the neighboring acetyl group took part in the reaction.<sup>174</sup>

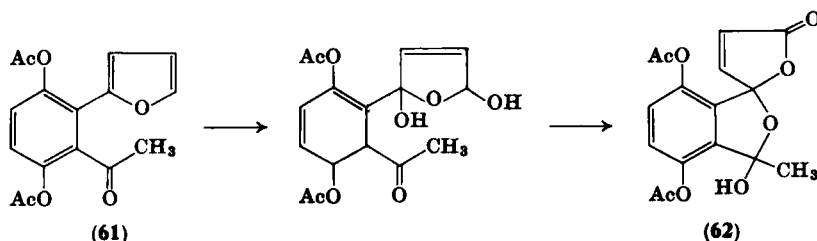
(a) Chromic acid oxidation of the leucoacetate (61) in acetic acid-water at 50° gave the sparingly soluble spiroketal lactone (62) in good yield. Initially 2,5 hydroxylation of the furan occurs, followed by

<sup>343</sup> H. Gilman, R. A. Franz, A. P. Hewlett, and G. F. Wright, *J. Am. Chem. Soc.* **72**, 3 (1950).

<sup>344</sup> N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.* **6**, 565 (1952).

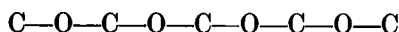
<sup>345</sup> W. Ried and W. Bodenstedt, *Ann.* **667**, 96 (1963).

half ketal formation, which is facilitated by the proximity of the acetyl group. Finally, the half acetal is oxidized to the lactone:

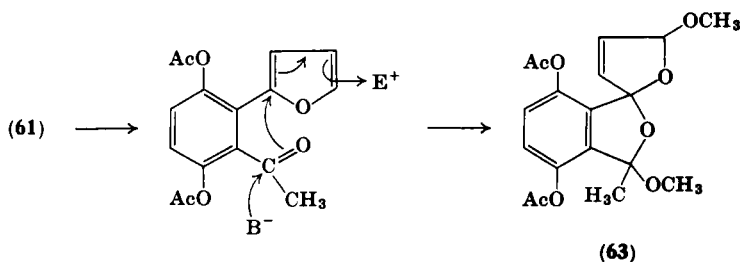


Both expected stereoisomers of **62** were found spectroscopically.

(b) Bromomethoxylation of the leucoacetate (**61**) at  $-10^\circ$  gave the spiroketalacetal (**63**), which is nicely crystalline. The structure of compound **63** contains the remarkable sequence:

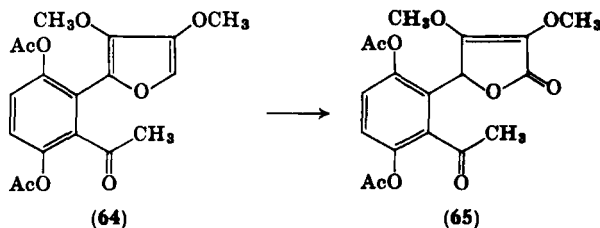


Obviously oxidation of the furan ring must occur again at the 2,5-position, with methanolysis of the  $\alpha$ -bromo compound to the full acetal<sup>174</sup>:

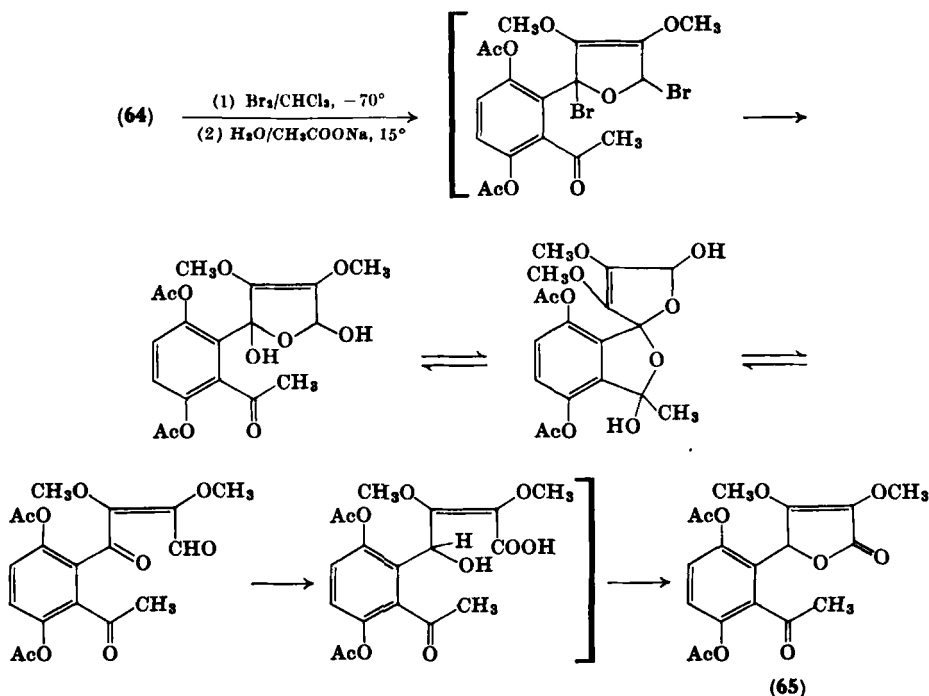


Four isomers are expected, but only two were found, and these were characterized spectroscopically.

(c) Bromination of the leucoacetate (**64**) occurred very rapidly at  $-70^\circ$  in chloroform. A crystalline compound (**65**) is obtained in almost quantitative yield, after solvolysis with excess of aqueous sodium acetate solution at room temperature. The product has one atom of oxygen more than the starting material and contains no halogen.<sup>174</sup>



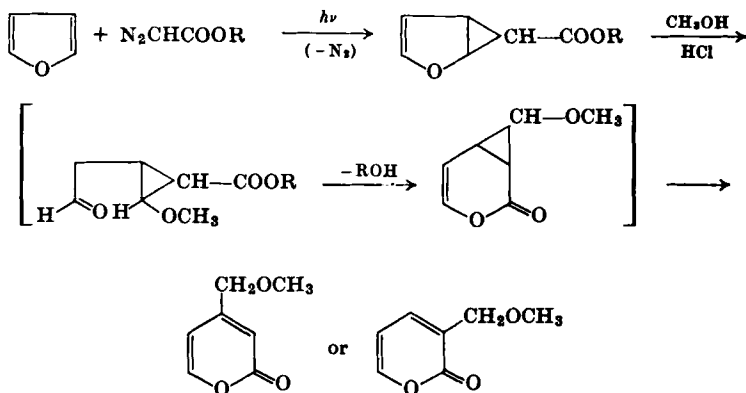
The migration of the double bond into the 3,4-position of the furan ring is presumably the result of a 2,5 oxidation. An intramolecular redox process must follow, perhaps under the influence of the base. The intermediates indicated in the following reaction scheme have not been proven:



Curiously, the identical lactone (65) is obtained when the leuco-acetate (63) is treated with oxygen in acetic anhydride and irradiated with light.<sup>174</sup>

E. INTO  $\alpha$ -PYRONES

Schenck and Steinmetz<sup>346</sup> described an example which can be mentioned here. An  $\alpha$ -pyrone derivative was obtained by a photochemical reaction of furan with diazoacetic ester:



## F. INTO MALEIC ANHYDRIDE

Oxidation of furan and its derivatives to give maleic anhydride has long been known.<sup>1</sup> Recently methods and the choice of suitable catalysts have been refined, and this results in increased yields. Thus, Costa Novella<sup>347</sup> oxidized furfural to maleic anhydride in 72% yield, with a Mo/V catalyst on  $\text{Al}_2\text{O}_3$ . Similar work is described by Hillers and Tarvida.<sup>348, 349</sup>

## G. HYDROGENOLYTIC CONVERSIONS

The hydrogenolysis of acylfurans in the gas phase at 200–300°, with group VIII metal catalysts on carbon carriers, can lead to

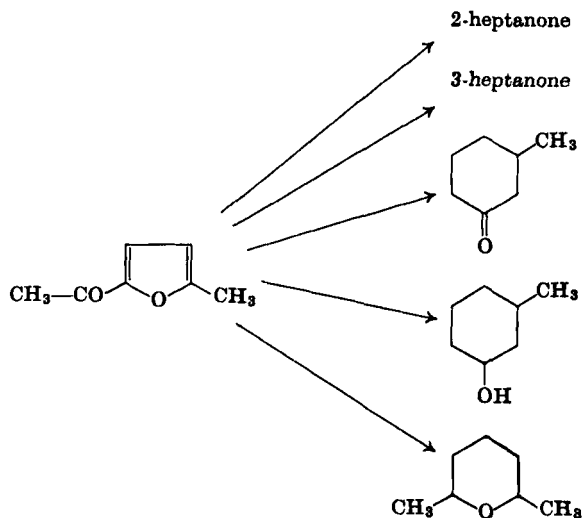
<sup>346</sup> G. O. Schenck and R. Steinmetz, *Angew. Chem.* **70**, 504 (1958).

<sup>347</sup> E. Costa Novella, R. Latre David, and V. Sánchez Lozano, *Anales Real Soc. Espan. Fis. Quim. (Madrid)* **52B**, 63 (1956); see *Chem. Abstr.* **50**, 13860 (1956).

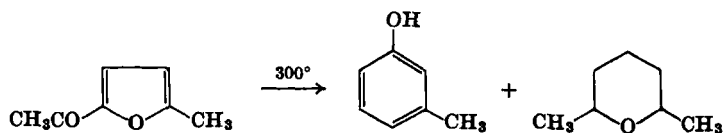
<sup>348</sup> P. Kalnins, S. Hillers, and M. Tarvida, *Latvijas PSR Zinatnu Akad. Vestis* p. 443 (1951); see *Chem. Abstr.* **48**, 9994 (1954).

<sup>349</sup> S. Hillers and M. Tarvida, *Latvijas PSR Zinatnu Akad. Vestis*, No. 11, 89 (1952); see *Chem. Abstr.* **49**, 279 (1955).

$\delta$ -diketones.<sup>230, 233, 350</sup> These can be cyclized to cyclohexanones or phenols, or via diols to tetrahydropyrans, e.g.:



At 300° 3-methylphenol is obtained in 40% yield, together with 2,6-dimethylpyran:



### VIII. Alkoxy-, Hydroxy-, and Aminofurans

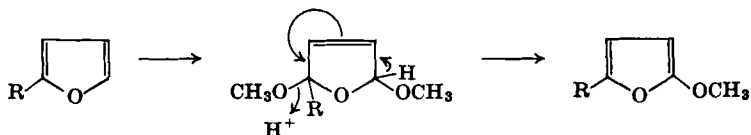
The results of recent work justify a summary. The interest centers on the tautomeric structure of these five-membered rings on the one hand, and on a new group of substances on the other.

#### A. ALKOXYFURANS

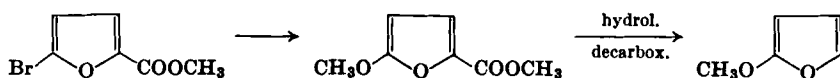
2-Alkoxyfurans are best prepared from 2,5-dialkoxy-2,5-dihydrofurans, by acid-catalyzed alcohol eliminations<sup>40, 242, 243</sup>:

<sup>350</sup> N. I. Shuikin, I. F. Bel'skii, and G. K. Vasilevskaya, *Zh. Obshch. Khim.* **32**, 2911 (1958); see *Chem. Abstr.* **58**, 9006 (1963).





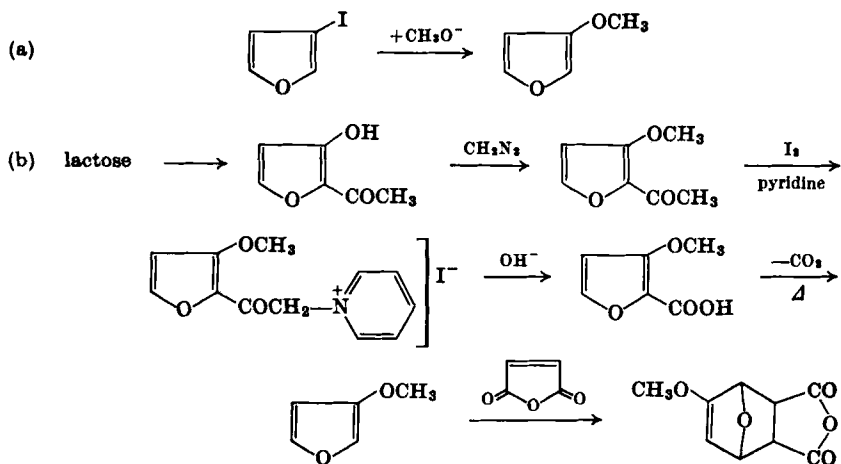
Nucleophilic substitution of 5-halo-2-furoic acid by methoxide, followed by decarboxylation, gave varying yields<sup>351</sup>:



2-Alkoxyfurans are unstable compounds. Monomethoxyfuran polymerizes in air. They react with active dienophiles; e.g., with maleic anhydride the expected substituted tetrahydro-3,6-epoxyphthalic anhydride was obtained, which can be aromatized exceptionally easily.

It is somewhat surprising that these furans are not particularly good dienophiles. However, this is not so in the case of 3-methoxyfurans, which are substantially more active dienes than furan.

Recently,<sup>252, 352</sup> 3-methoxyfuran has been synthesized by the following two methods:



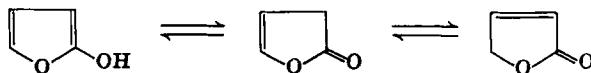
<sup>351</sup> E. D. Amstutz and R. J. Petfield, *J. Org. Chem.* **19**, 1944 (1954).

<sup>352</sup> S. Gronowitz and G. Sörlin, *Acta Chem. Scand.* **15**, 1419 (1961).

The first method uses 3-iodofuran as starting material, which is not readily accessible. The other uses isomaltol, which can be prepared from lactose in two steps. The longer method, on the other hand, goes via stages which are reproducible, and according to our experience the yields are satisfactory. 3,4-Dimethoxyfuran shows a very high diene activity which has been mentioned in Section IV, B.

## B. HYDROXYFURANS

The existence of 2-hydroxyfurans as distinct compounds has been proposed. However, this has not been shown in a single case experimentally (see Dunlop and Peters<sup>1</sup> for a discussion of these compounds).



These compounds exist not as furans but as  $\beta,\gamma$ - or  $\alpha,\beta$ -butenolides.

The situation with 3-hydroxyfurans was rather uncertain until recently. As a result of new work, the situation has been clarified. The so-called "3-hydroxyfuran" was often discussed in the literature.<sup>1, 353</sup> Thus, it has been described<sup>354</sup> as a phenolic, crystalline compound, m.p. 58°, which allegedly gives a normal adduct with maleic anhydride. However, these observations were considered unreliable, as Bailey and Waggoner<sup>355</sup> could not reproduce the results. Support for the latter workers was given also by Mabry,<sup>342</sup> who again failed to reproduce the results. In the course of work on the synthesis of muscarine, the whole problem was undertaken on a broader basis. Intermediates were obtained which could have been 3-hydroxyfurans, but they were unequivocally described as  $\alpha,\beta$ -unsaturated ketones.<sup>356, 357</sup>

The results can be summarized as follows<sup>19, 358</sup>:

<sup>353</sup> R. H. Thompson, *Quart. Rev.* **10**, 34 (1956).

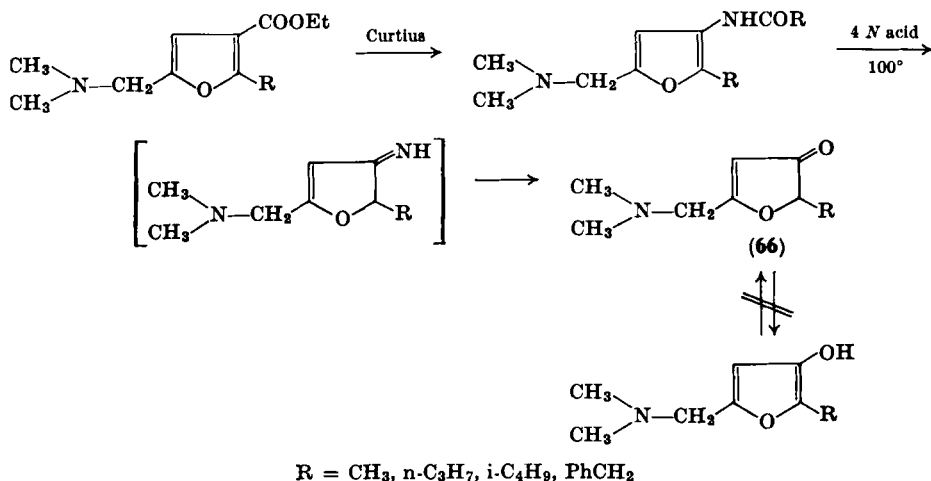
<sup>354</sup> H. H. Hodgson and R. R. Davies, *J. Chem. Soc.* pp. 806 and 1013 (1939).

<sup>355</sup> P. S. Bailey and J. V. Waggoner, *J. Org. Chem.* **15**, 159 (1950).

<sup>356</sup> C. H. Eugster, *Helv. Chim. Acta* **40**, 2462 (1957).

<sup>357</sup> C. H. Eugster, F. Häfziger, R. Denss, and E. Girod, *Helv. Chim. Acta* **41**, 205 (1958).

<sup>358</sup> C. H. Eugster, K. Allner, and R. E. Rosenkranz, *Chimia (Aarau)* **15**, 516 (1961).

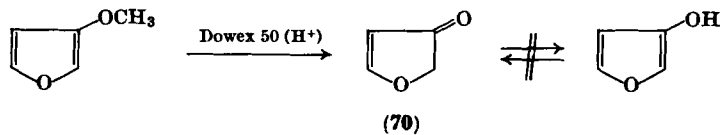
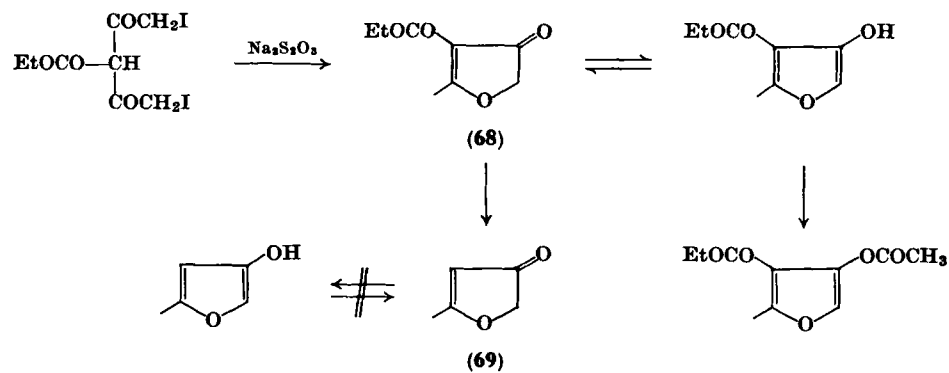
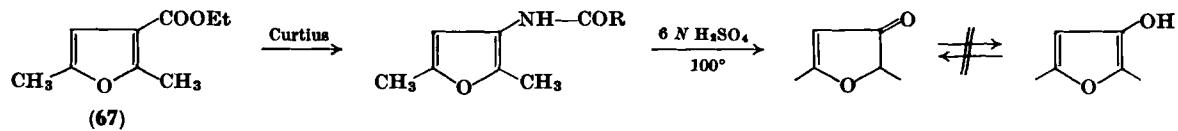


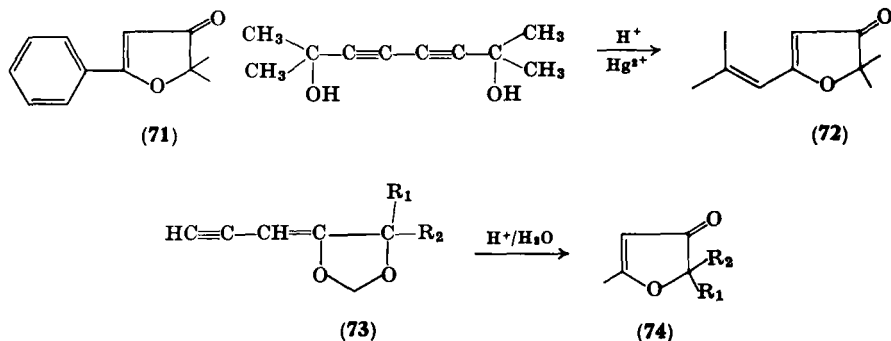
**66** is obtained by strong *acidic* hydrolysis of the compounds which result from the Curtius degradation of the basically substituted 3-furoic ester. It has been shown by chemical and spectroscopic evidence (UV, IR, NMR) to be purely an  $\alpha,\beta$ -unsaturated ketone, with no trace of the enolic form. It was realized that the strongly basic side chain could influence the results, but it also proved possible to synthesize the following compound without a basic substituent:

2,5-Dimethyl-3-furoic ester (**67**) also undergoes the Curtius degradation. The urethan which is formed can be hydrolyzed by strong acid to a neutral oil, which has an intense smell, similar to that of freshly baked bread. It was an  $\alpha,\beta$ -unsaturated ketone with the same spectroscopic properties as the basic homologs. **68** can be regarded as a ketone as well, although it probably has a small enol content, since base-catalyzed acetylation leads to the enol acetate without difficulty. Acid hydrolysis of **68** and decarboxylation yields the monomethyl ketone **69**. Finally, the unsubstituted "3-hydroxyfuran" (**70**) was successfully prepared recently<sup>359</sup> by careful hydrolysis of 3-methoxyfuran. According to its spectrum it is also completely in the  $\alpha,\beta$ -unsaturated keto form.

All these  $\alpha,\beta$ -unsaturated ketones mentioned show UV and IR spectra almost identical with those of 5-disubstituted compounds, where of course no enolization is possible:

<sup>359</sup> A. Hofmann and C. H. Eugster, *Helv. Chim. Acta* **48**, 1322 (1965).





A number of compounds substituted in this way were prepared. Thus Meister<sup>360</sup> obtained **74** by the hydrolysis of dioxolan (**73**). Bullatenone (**71**), which is obtained from *Myrtus bullata*,<sup>361, 362</sup> is very similar, in spite of the additional conjugation with the phenyl ring, as is the compound **72**, which is prepared by the hydration of a diynediol.<sup>363</sup> The structure of a similar compound, prepared also from an acetyleneglycol,<sup>364</sup> is not exactly known.

The typical properties of 3(2H)-furanones are as follows.

The IR spectrum shows a characteristic and very intense pair of bands at 1710 and 1610  $\text{cm}^{-1}$  (double bond and carbonyl).

In the case of compounds with fewer substituents, e.g. **69** and **70**, the bands at shorter wavelength are split (1742/1707  $\text{cm}^{-1}$  or 1733/1706  $\text{cm}^{-1}$  in  $\text{CCl}_4$  solution).

All dihydrofuranones show strong absorption in the UV at about 260  $\text{m}\mu$  ( $\epsilon$  has values up to 12,000), and additional conjugation has a marked effect. The absorption is not affected by the addition of acids or tertiary bases to the dilute solution.

The NMR spectra are discussed in Refs. 19 and 359.

Chemically, the properties which are most interesting are their unusual *acid stability* and high *alkali lability*. Compounds which are

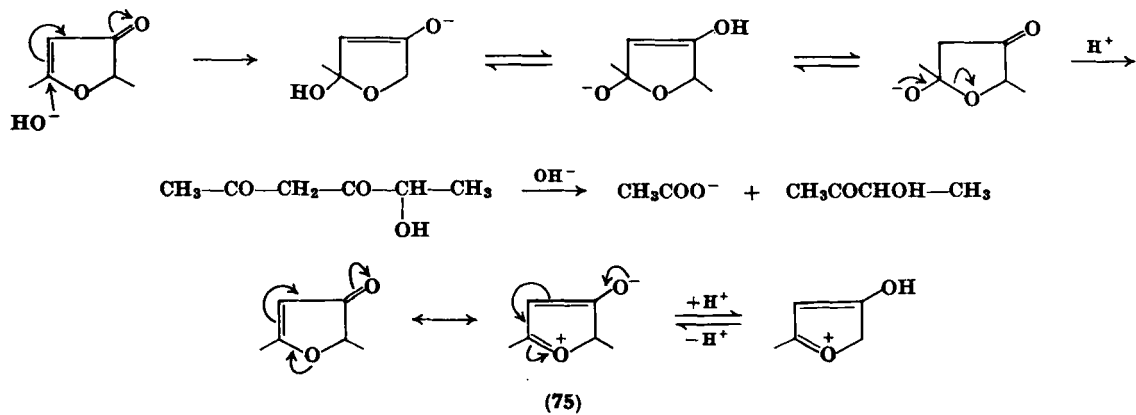
<sup>360</sup> H. Meister, German Patent 1,147,593 (1960); see *Chem. Abstr.* **59**, 11427 (1963).

<sup>361</sup> C. W. Brandt, W. I. Taylor, and B. R. Thomas, *J. Chem. Soc.* p. 3245 (1954).

<sup>362</sup> W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.* p. 3871 (1958).

<sup>363</sup> F. Bohlmann, *Ber.* **94**, 1104 (1961).

<sup>364</sup> V. M. Al'bitskaya and E. D. Venus-Danilova, *Zh. Obshch. Khim.* **30**, 349 (1960); see *Chem. Abstr.* **54**, 22558 (1960).

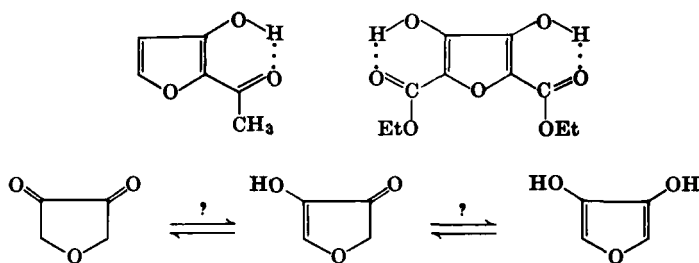


disubstituted in 5 show a pronounced ability to reduce Nessler's, Fehling's, and Tollens' reagents. The ferric chloride test is positive, but as oxidation processes take place the reaction is not diagnostic of an actual enol content. The alkaline degradation of dimethyl-dihydrofuranone gives acetate ion and acetoin.

These new compounds are distinguished from dihydrofurans, which are genuine enol ethers, by their acid stability. It therefore seems appropriate to give these new compounds a distinct name, and  $\Delta^2$ -furenidone-4 seems to be suitable. This is obviously not an enol ether, but a vinylogous lactone, and so the limiting structure (75) may possibly contribute substantially to the ground state of the furenidone.

At least some protonation at C-4 would be expected.

Furenidones are similar to  $\gamma$ -pyrones in certain of their chemical properties. *Isomaltol* has already been mentioned, and it is the odoriferous material found in bread. Hodge and co-workers<sup>365</sup> recently elucidated its structure. Its properties indicate that it has an enolic character without doubt ( $pK_{H_2O}^* 5.60$ ; purple color in the ferric chloride reaction; *O*-methylation by  $CH_2N_2$ ; stable to alkali; labile to acid; UV, IR, NMR measurements<sup>19</sup>). *Isomaltol* is therefore a genuine 3-hydroxyfuran, as is 3,4-dihydroxyfuran-2,5-dicarboxylic ester, which has been known for a long time.



Both of the above-mentioned compounds can undergo very pronounced intramolecular hydrogen bonding, in the same sense as a "conjugated chelate system."<sup>366, 367</sup>

*3,4-Diketotetrahydrofuran* was prepared by Kendall and Hajos<sup>368</sup>

<sup>365</sup> J. E. Hodge and E. C. Nelson, *Cereal Chem.* **38**, 207 (1961).

<sup>366</sup> I. M. Hunsberger, R. Ketcham, and H. S. Gutowsky, *J. Am. Chem. Soc.* **74**, 4839 (1952).

<sup>367</sup> L. J. Bellamy, *J. Chem. Soc.* p. 4487 (1954).

<sup>368</sup> E. C. Kendall and Z. G. Hajos, *J. Am. Chem. Soc.* **82**, 3219 (1960).

from  $\omega,\omega'$ -dibromodiacetyl. This compound undoubtedly contains none of the enol form (yellow prisms;  $\lambda_{\max}$  520  $m\mu$ ; IR 1780  $\text{cm}^{-1}$ ; NMR, singlet at  $\tau = 5.5$ ).

### C. AMINOFURANS

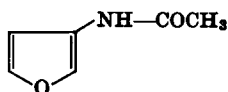
3-Acylaminofurans will be mentioned here. They were isolated by Kuhn and co-workers from the products of the Morgan–Elson reaction.<sup>369</sup>

When *N*-acetyl-D-glucosamine is heated with dilute sodium carbonate solution a colorless “chromogen” is formed. The latter yields a violet dyestuff<sup>370</sup> with *p*-dimethylaminobenzaldehyde in acidic solution. This reaction is the basis of the quantitative determination of *N*-acetyl amino sugars (Morgan–Elson reaction).

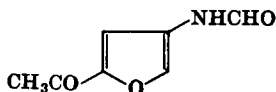
Chromatographic experiments on the formation of the chromogen shows that three chromogens were formed in the presence of each other, and they were called I, II, and III by Kuhn *et al.* Chromogen III forms only in small yield, by the action of hot dilute sodium carbonate solution on *N*-acetyl-D-glucosamine. It is formed in larger yield when *N*-acetylglucosamine is refluxed with pyridine. 3-Acetamidofuran also forms in small quantity.

The structure of chromogen III from the Morgan–Elson reaction is elucidated by the synthesis shown on the following page.

3-Acetamidofurans can be coupled with diazonium salts and with *p*-dimethylaminobenzaldehyde to give dyestuffs. This also occurs with:



which has been prepared from 3-furoic acid,<sup>371</sup> and for the following compound<sup>124</sup>:

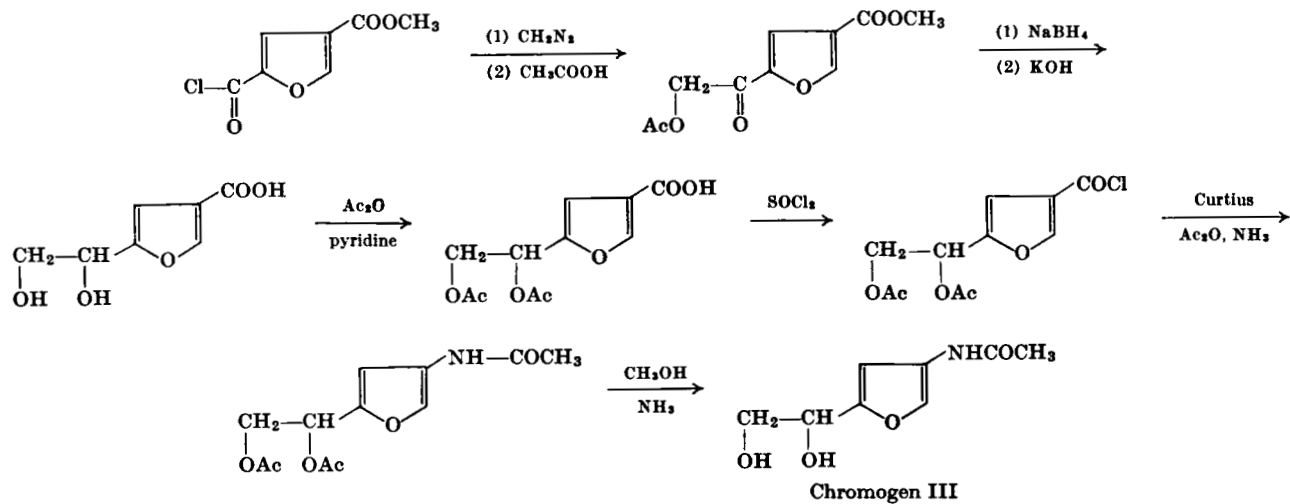


<sup>369</sup> A. B. Foster and D. Horton, *Advan. Carbohydrate Chem.* **14**, 213 (1959).

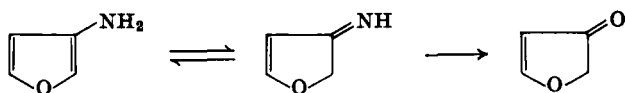
<sup>370</sup> R. Kuhn and G. Krüger, *Ber.* **90**, 264 (1957).

<sup>371</sup> R. Kuhn and G. Krüger, *Ber.* **89**, 1473 (1956).





3-Aminofurans are probably completely in the imino form:

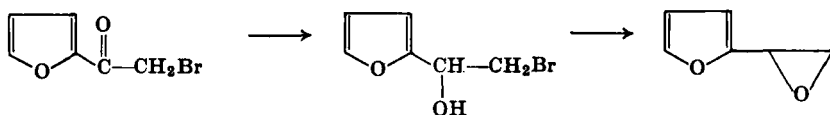


although no physicochemical measurements seem to have been made on these very sensitive compounds. As has already been mentioned, they are used for the preparation of "3-hydroxyfurans," as the result of hydrolysis, which readily takes place.

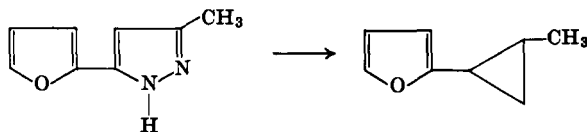
### IX. Some Furan Derivatives

In this section, certain furans which contain interesting substituents will be discussed.

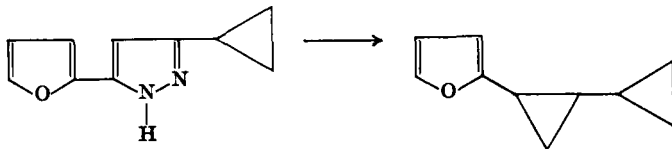
*2-Epoxyvinylfuran* was prepared in 55% yield by Novitskii and co-workers<sup>371a</sup> from 2-bromoacetylfuran, by borohydride reduction and treatment with alkali:



Glukhovtsev *et al.*<sup>130</sup> obtained *methylfurylcyclopropane* in 90% yield, by treating 3-methyl-5-(2-furyl)pyrazole with alkali:

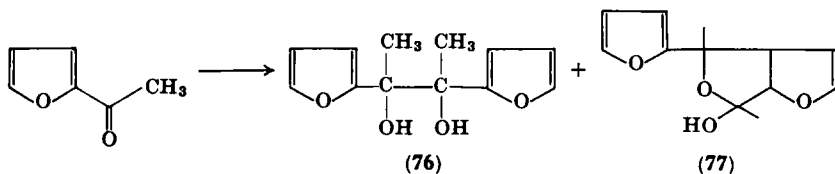


The following compound was prepared analogously:

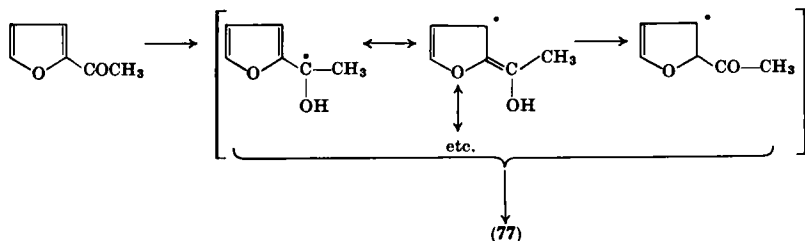


<sup>371a</sup> K. Yu. Novitskii, A. F. Oleinik, and Yu. K. Yur'ev, *Zh. Obshch. Khim.* **33**, 1043 (1963); see *Chem. Abstr.* **59**, 8682 (1963).

Wiemann and co-workers<sup>372</sup> observed that 2-acetylfuran underwent an interesting reaction when treated with zinc and acetic acid. They obtained two isomeric products, **76** and **77** with very different structures:



**76** is the result of a normal pinacol reduction. However, the authors believe that the formation of **77** is the result of a radical mechanism, which they formulate as:



It should be noted that a radical substitution in the 3-position of the furan ring has been observed in only a very few cases. In particular, 2-furoic acid is arylated in the 5-position.<sup>158</sup>

Arbuzov and Zoroastrova<sup>373</sup> described the conversion of furfural to difurylethylene, in the presence of triethyl- or triisopropylphosphite.

*Kinetin* (6-furfurylaminopurine) aroused interest because it has the ability to stimulate the cell division of certain plant seedlings. It has not been shown whether it is a genuine natural product, as it can be isolated from artificially altered desoxyribonucleic acid. This shows that it forms by the reaction of adenine with 2-desoxy-D-ribose.<sup>374, 375</sup>

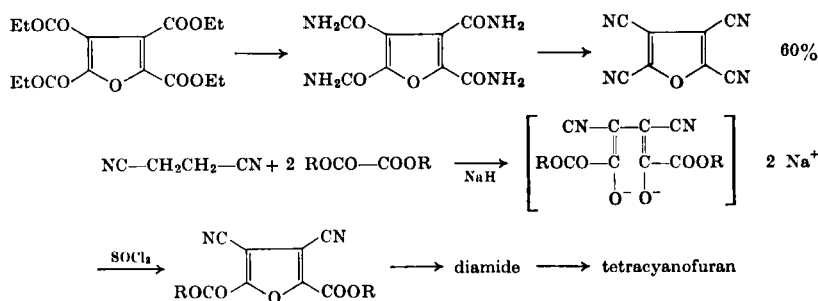
<sup>372</sup> J. Wiemann, J. P. Morizur, and G. Dana, *Compt. Rend.* **257**, 1300 (1963).

<sup>373</sup> B. A. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nauk SSSR* p. 1030 (1960); see *Chem. Abstr.* **54**, 24627 (1960).

<sup>374</sup> R. H. Hall and R. S. de Ropp, *J. Am. Chem. Soc.* **77**, 6400 (1955).

<sup>375</sup> R. Hull, *J. Chem. Soc.* p. 2746 (1958).

*Tetracyanofuran* has recently been prepared by Weis<sup>376</sup> in the following ways:



Tetracyanofuran is a colorless, crystalline substance, which is extremely sensitive to bases. The reactivity of the 2,5-cyano groups is different from that of the 3,4 groups.

*Furan tetracarboxylic acid* aroused interest as it is a remarkably strong acid, with an acidity comparable to that of mellitic acid. The mono salt is stable to HCl<sup>377</sup>:

$$pK_a$$

$K_1$	$K_2$	$K_3$	$K_4$
0.38	1.10	2.73	6.71

The tetracarbethoxy compound shows carbonyl bands at very short wavelengths in the IR: 1766s, 1759w, 1747s, 1728s, 1612s  $\text{cm}^{-1}$  in nujol.

According to Le Fèvre *et al.*<sup>378</sup> furfural shows the *s-trans*-conformation in solution. On the other hand, according to these authors, furil is not planar, but has an azimuthal angle of 118.5°.


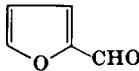
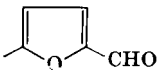
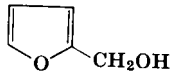
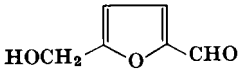
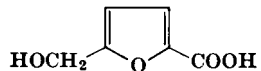
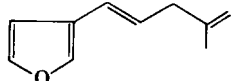
## X. Naturally Occurring Furan Derivatives

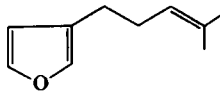
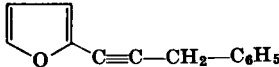
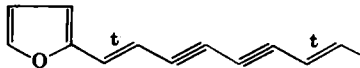
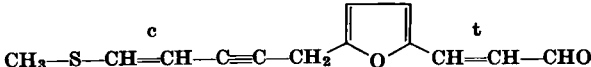
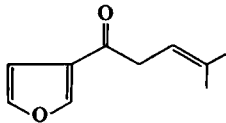
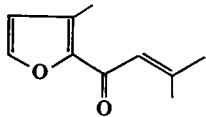
The following table contains those naturally occurring furan derivatives which have recently been found, isolated, or elucidated. The name, origin, and structure are given in each case, and the references are kept to a minimum.

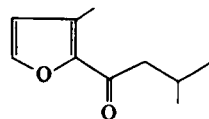
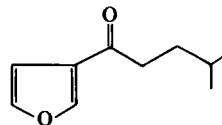
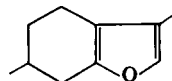
<sup>376</sup> C. D. Weis, *J. Org. Chem.* **27**, 3514 (1962).

<sup>377</sup> W. Cocker, W. J. Davis, T. B. H. McMurtry, and P. A. Start, *Tetrahedron* **7**, 299 (1959).

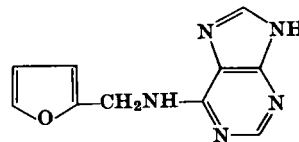
<sup>378</sup> P. H. Cureton, C. G. Le Fèvre, and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 4447 (1961).

Name	Origin	Structure	References*
2-Methylfuran	Oil of turpentine		379 (No. 1776)
Furfural	<i>Codium fragile</i> , <i>Digenea simplex</i> , roasted coffee		380, 381, 382, 379 (No. 1782)
5-Methylfurfural	<i>Codium fragile</i> , <i>Digenea simplex</i> , roasted coffee, oil of tobacco leaves		380, 381, 382, 383, 379 (No. 1783)
Furfuryl alcohol	<i>Codium fragile</i> , roasted coffee		380, 382, 379 (No. 1781)
5-Hydroxy-methylfurfural	Oil of tobacco leaves, roasted coffee		383, 382
5-Hydroxy-methyl-2-furoic acid	<i>Gibberella fujikuroi</i>		384, 379 (No. 1788a)
Clausenane	Leaves of <i>Clausenia willdenovii</i>		385, 379 (No. 1778)

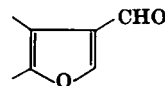
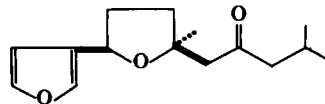
Name	Origin	Structure	References <sup>a</sup>
Perillene	<i>Perilla citriodora</i>		379 (No. 1777)
Carlina oxide	Oil of <i>Carlina acaulis</i>		386, 379 (No. 1779)
Atractylodin	Oil of the roots of <i>Atractylodes mandschurei</i>		387
Unnamed compound	<i>Chrysanthemum coronarium</i>		388
Egomaketone	<i>Perilla frutescens</i>		389
Naginata ketone ( $\beta$ -dehydroelsholzione)	<i>Perilla frutescens</i> , <i>Elsholtzia cristata</i>		390, 391

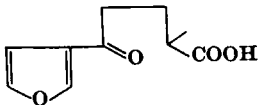
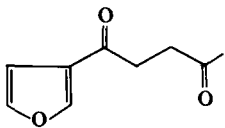
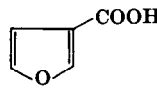
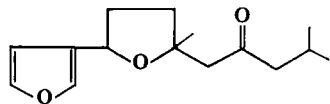
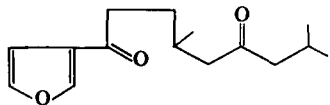
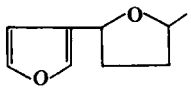
Elsholtzia ketone    *Perilla frutescens*379  
(No. 1785)Perillaketone    *Perilla frutescens*392, 379  
(No. 1786)Menthofuran    *Mentha* sp.379  
(No. 1780)

Kinetin    Coconut (genuine?)

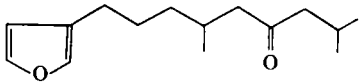
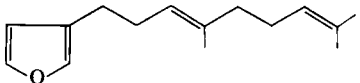
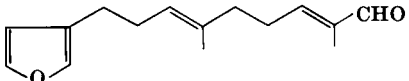
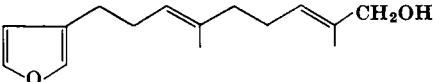
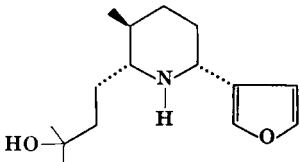
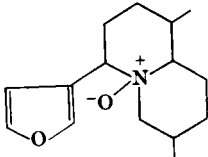


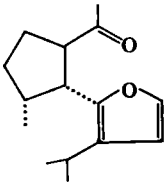
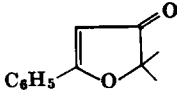
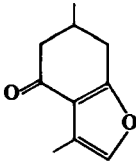
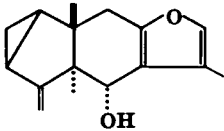
393

4,5-Dimethyl-  
furan-3-alde-  
hyde379  
(No. 1784)(+) -Ipomeamar-  
one    Sweet potatoes, infected  
with *Ceratostomella*  
*fimbriata*394, 379  
(No. 1792)

Name	Origin	Structure	References <sup>a</sup>
Batatic acid	Sweet potatoes, infected with <i>Ceratostomella fimbriata</i>		394, 379 (No. 1789)
Ipomeanine	Sweet potatoes, infected with <i>Ceratostomella fimbriata</i>		394, 379 (No. 1787)
3-Furoic acid	Sweet potatoes, infected with <i>Ceratostomella fimbriata</i>		394, 379 (No. 1788)
(-)-Ngaione (antipode of ipomeamarone)	<i>Myoporium laetum</i> , <i>M. acuminatum</i> , <i>Eremophila latrobei</i>		394, 379 (No. 1793)
Myoporone	<i>Myoporium bontioides</i>		394, 395
Unnamed compound	Fusel oil from sweet potatoes		396

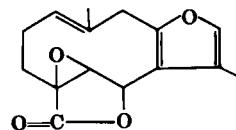


Unnamed compound	Fusel oil from sweet potatoes		396
Dendrolasin	<i>Lasius</i> ( <i>Dendrolasius</i> ) <i>fuliginosus</i> , <i>Torreya nucifera</i>		397, 398
Torreyal	<i>Torreya nucifera</i>		398
Torreyol	<i>Torreya nucifera</i>		398
Nupharamine	<i>Nuphar japonicum</i>		399
Nupharidine	<i>Nuphar japonicum</i>		400

Name	Origin	Structure	References*
Pelargon A	<i>Geranium bourbon</i>		401, 402
Bullatenone	<i>Myrtus bullata</i>		362
Evodone	<i>Evodia hortensis</i>		403, 404, 379 (No. 1787a)
Linderene	<i>Lindera strychninifolia</i>		405

Linderane

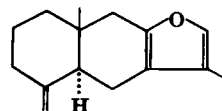
*Lindera strychnifolia*



406

Atractylon

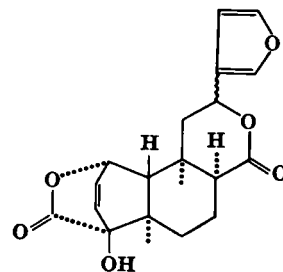
*Atractylodes japonica*



407

Columbin

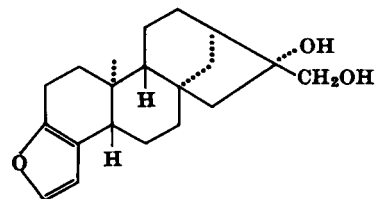
*Jatrorrhiza palmata*



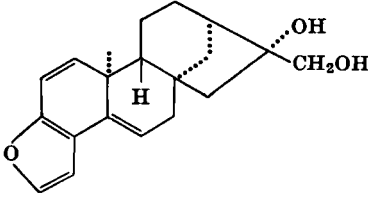
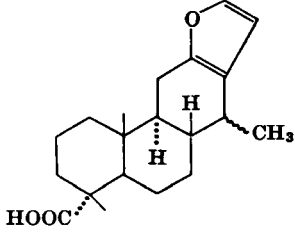
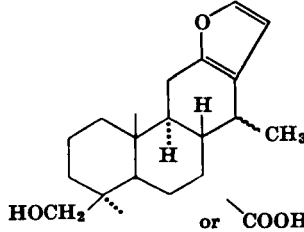
408, 409,  
410, 379  
(No. 1146a)

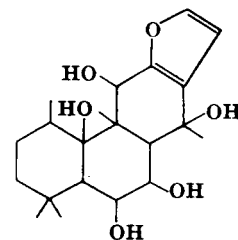
Cafestol

Coffee oil



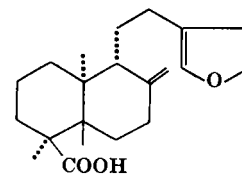
411, 412,  
413, 379  
(No. 1965a)

Name	Origin	Structure	References <sup>a</sup>
Kahweol	Coffee oil		411
Vinhaticoic acid	<i>Plathymenia reticulata</i>		414, 415, 379 (No. 1963)
Vouacapenyl alcohol and vouacapenic acid	<i>Vouacapoua macropetala</i> , <i>V. americana</i>		416, 415, 379 (Nos. 1964, 1965)

$\gamma$ -Caesalpin*Caesalpinia bonducella*

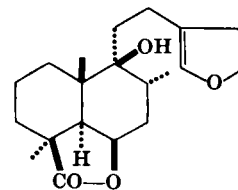
417

Polyalthic acid

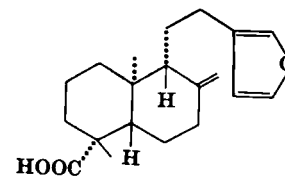
*Polyalthia fragrans*

418

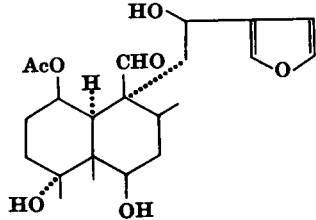
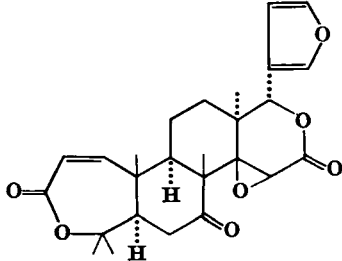
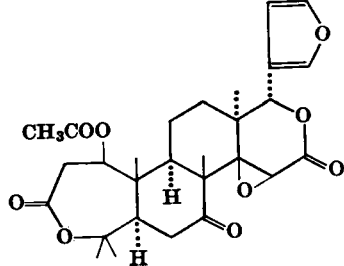
Marrubiin

*Marrubium vulgare*419, 379  
(No. 1957)

Daniellic acid

*Daniellia oliveri*

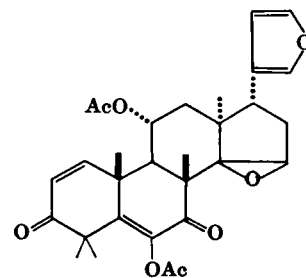
420

Name	Origin	Structure	References <sup>a</sup>
Cascarillin	<i>Croton eluteria</i>		421
Casimirolid (obacunone)	<i>Phellodendron amurense</i>		422
Nomilin	<i>Citrus</i> seed		423

Anthothecol

*Khaya anthotheca*

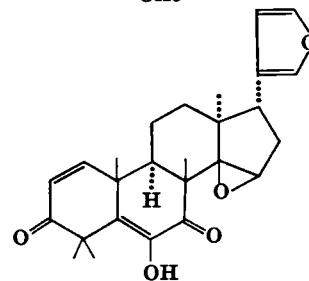
424



Cedrelone

*Cedrela toona*

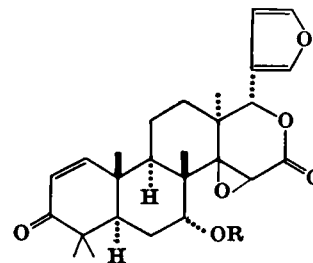
425

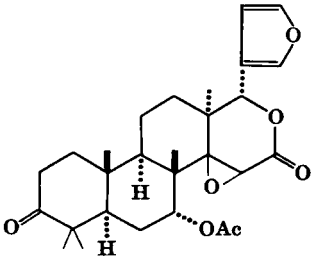
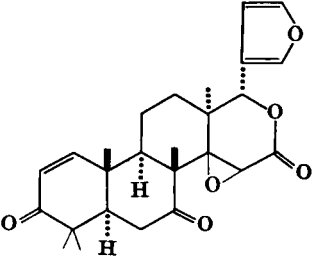
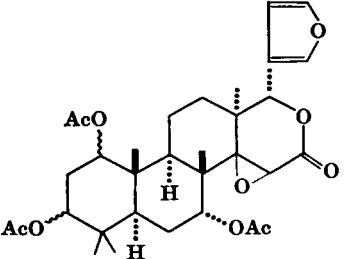


Gedunin

*Entandrophragma angolense*

426

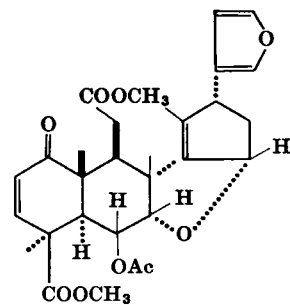


Name	Origin	Structure	References <sup>a</sup>
Dihydrogedunin	<i>Guarea thompsonii</i>		424
Deacetoxy-7-oxogedunin	<i>Cedrela odorata</i>		424
Khivorin	<i>Khaya ivorensis</i> and <i>Khaya grandifolia</i>		424



Nimbin

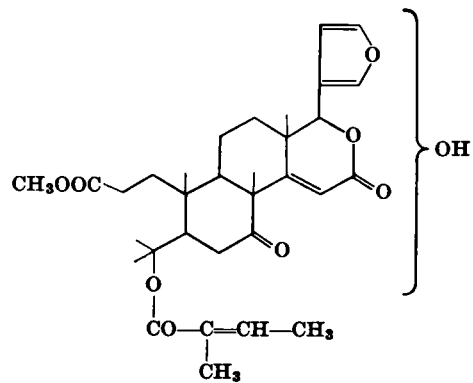
*Melia indica*



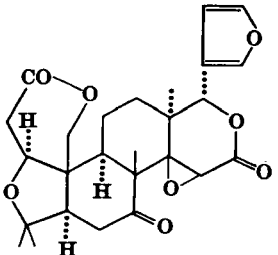
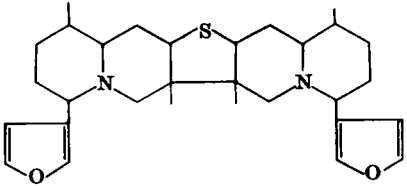
427, 428

Swietenin

*Swietenia macrophylla*



429

Name	Origin	Structure	References <sup>a</sup>
Limonin	Lemon seed and seeds of various <i>Citrus</i> species		423
Thiobinupharidin, <i>Nuphar luteum</i> neothiobinupharidin			430

<sup>a</sup> Numbers in parentheses appear in Ref. 379.

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## Appendix

Further naturally occurring furan compounds (without formulas given):

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Andirobin	Seeds of <i>Carapa guayanensis</i> Aubl. [W. D. Ollis, A. D. Ward, and R. Zelnik, <i>Tetrahedron Letters</i> p. 2607 (1964)]
Cacalol, cacalon	Root of <i>Cacalea decomposita</i> [A. Gray, J. Romo, and P. Joseph-Nathan, <i>Tetrahedron</i> <b>20</b> , 2331 (1964)]
Cascarillin A	<i>Cascarilla</i> bark [T. G. Halsall, A. W. Oxford, and W. Rigby, <i>Chem. Commun.</i> p. 218 (1965)]
Castoramin	<i>Castoreum</i> [Z. Valenta and A. Khaleque, <i>Tetrahedron Letters</i> <b>12</b> , 1 (1959)]
Deacetylnomilin (isolimonin?)	Seeds of various <i>Citrus</i> species, <i>Poncirus trifoliata</i> [D. L. Dreyer, <i>J. Org. Chem.</i> <b>30</b> , 749 (1965)]
Dehydrodeoxynupharidin	<i>Nuphar japonicum</i> D.C. [Y. Arata, <i>Chem. Pharm. Bull. Japan</i> , <b>12</b> , 1394 (1964)]
Deoxylimonin	Seeds of <i>Citrus paradisi</i> (grapefruit) [D. L. Dreyer, <i>J. Org. Chem.</i> <b>30</b> , 749 (1965)]
Deoxynupharadin	<i>Nuphar luteum</i> (rhizomes) [O. Achmatowicz and Z. Bellen, <i>Tetrahedron Letters</i> p. 1121 (1962)]
Dimethyl sciadinonate, sciadinone	Wood and leaves of <i>Sciadopitys verticillata</i> Sieb. et Zucc. [C. Kaneko, T. Tsuchiya, and M. Ishikawai, <i>Chem. Pharm. Bull. Japan</i> <b>11</b> , 271 (1963)]
Various simple furan compounds	Coffee oil (aroma) [M. A. Gianturco, A. S. Giammarino, P. Friedel, and V. Flanagan, <i>Tetrahedron</i> <b>20</b> , 2951 (1964)]
Furanoeremophilone, albopetasin, petasalbin	<i>Petasites albus</i> , <i>P. spurius</i> [L. Novotný, V. Herout, and F. Šorm, <i>Collection Czech. Chem. Commun.</i> <b>29</b> , 1400 and 2462, and 2189 (1964); <i>Tetrahedron Letters</i> p. 697 (1961)]
Furanopetasin	<i>Petasites officinalis</i> [L. Novotný, J. Jizba, V. Herout, and F. Šorm, <i>Collection Czech. Chem. Commun.</i> <b>27</b> , 1393 (1962); <b>29</b> , 1923 (1964)]
Furanopelargon A, furanopelargon B	Oil from <i>Geranium bourbon</i> [G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, <i>Tetrahedron</i> <b>20</b> , 1789 (1964); M. Romaňuk, V. Herout, F. Šorm, Y.-R. Naves,

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- P. Tullen, R. B. Bates, and C. W. Sigel, *Collection Czech. Chem. Commun.* **29**, 1048 (1964)]
- Furoguaiacin, methyl-furoguaiacin Wood of *Guaiacum officinale* L., *G. sanctum* [F. E. King and J. G. Wilson, *J. Chem. Soc.* p. 4011 (1964)]
- Hardwickia acid *Hardwickia pinnata* [R. Misra, R. C. Pandey, and Sukh Dev, *Tetrahedron Letters* p. 3751 (1964)]
- Isoegomaketone *Perilla frutescens* var. *crispa* f. *discolor* [H. Ito, *Yakugaku Zasshi* **84**, 1123 (1964)]
- Linderalactone, isolinderalactone, lindestrene, linderenacetate Roots of *Lindera strychninifolia* Vill. [K. Takeda, H. Minato, M. Ishikawa, and M. Miyawaki, *Tetrahedron* **20**, 2655 and 2991 (1964); *J. Chem. Soc.* p. 4578 (1964)]
- Methyl angolensate Wood of *Entandophragma angolense*, *Cedrela odorata*, *Guarea thompsonii* [C. W. L. Bevan, J. W. Powell, D. A. H. Taylor, P. Toft, and M. Welford, *Chem. Ind. (London)* p. 1751 (1964)]
- Mexicanolide, cedrela substance B *Cedrela mexicana*, *C. odorata* [J. D. Connolly, R. McCrindle, and K. H. Overton, *Chem. Commun.* p. 162 (1965); C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *ibid.* p. 281 (1965)]
- Nuphamin *Nuphar japonicum* D.C. [Y. Arata and T. Ohashi, *Chem. Pharm. Bull. Japan* **13**, 392 (1965)]
- Nuciferol, neotorreyol Wood oil from *Torreya nucifera* Sieb. et Zucc. [T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Soc. Chim. Japan* **38**, 381 (1965)]
- Palmarin, chasmanthin, jateorin Colombo root [S. K. Balasubramanian, D. H. R. Barton, and L. M. Jackman, *J. Chem. Soc.* p. 4816 (1962)]
- Salannin Seed oil from *Melia azadirachta* [R. Henderson, R. McCrindle, K. H. Overton, and A. Melera, *Tetrahedron Letters* p. 3969 (1964)]
- Sciadin *Sciadopitys verticillata* Sieb. et Zucc. [M. Sumimoto, *Tetrahedron* **19**, 643 (1963); *Chem. Pharm. Bull. Japan* **11**, 271 (1963)]
- Tinophyllon *Tinomisium philippinense* Diels [G. Aguilar-Santos, *Chem. Ind. (London)* p. 1074 (1965)]
- Veprison Bark of *Vepris bilocularis* Engler [T. R. Govindachari, B. S. Joshi, and V. N. Sundararajan, *Tetrahedron* **20**, 2985 (1964)]
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